Saudi Journal of Ophthalmology (2011) **25**, 389–394

King Saud University

Saudi Journal of Ophthalmology

www.saudiophthaljournal.com
www.ksu.edu.sa
www.sciencedirect.com

GLAUCOMA UPDATE

Antiglaucoma drugs: The role of preservative-free formulations

Alessandro Bagnis, MD, PhD; Marina Papadia, MD, PhD; Riccardo Scotto, CO; Carlo E. Traverso, MD *

Eye Clinic, Department of Neurosciences, Ophthalmology and Genetics, University of Genova, Genova, Italy

Received 6 August 2011; revised 18 August 2011; accepted 24 August 2011
Available online 28 August 2011

KEYWORDS

Glaucoma medications;
Benzalkonium chloride;
Preservative-free formulations;
Ocular surface toxicity;
Compliance

Abstract Hypersensitive reactions to eyedrops are a common finding in clinical practice and represent a frequent cause of discontinuation of the therapy. Moreover, experimental and clinical studies show that long term use of topical drugs may induce ocular surface changes causing discomfort and potentially negatively affecting the compliance to the treatment as well as the success rate of filtering procedures. The exact mechanism involved and the roles of the active compound and the preservatives in inducing such detrimental effects of ophthalmic solutions are unclear. During the last years several antiglaucoma agents have been marketed as either preservative-free or benzalkonium chloride-free formulations in an attempt to reduce the adverse effects related to preservatives. This paper summarizes the body of evidence from existing studies about preservatives in antiglaucoma eyedrops, focusing on the latest compounds commercially available. A systematic review of the literature was performed.

Current research is focusing not only on the efficacy of the drugs but also on their tolerability. Based on the existing data, there is a rationale to support the use of benzalkonium-free solutions whenever possible, especially in patients suffering from concomitant ocular surface diseases, experiencing local side effects and in those expected to need multiple and prolonged topical treatments.

* Corresponding author. Address: Clinica Oculistica, Università di Genova, Viale benedetto XV, 16132 Genova, Italy. Tel.: +39 0103538469; fax: +39 0103538494.
E-mail addresses: alebagnis@libero.it, mc8620@mclink.it (C.E. Traverso).

Peer review under responsibility of King Saud University.
doi:10.1016/j.sjopt.2011.08.004

Production and hosting by Elsevier

Contents

1. Introduction

Glaucoma is a group of ocular diseases with multifactorial aetiology characterized by a clinically characteristic optic neuropathy and associated visual field loss (Falkenberg and Bex, 2007). The vast majority of glaucomatous patients are older than 60 years, and due to longer life expectancy, the prevalence of glaucoma is increasing worldwide (Coleman, 1999).

The relative risk to develop glaucoma rises continuously with the level of the intra-ocular pressure (IOP); however, there is no evidence of a threshold IOP for the onset of the disease (European Glaucoma Society, 2008a).

Primary open-angle glaucoma (POAG), the most common form of the disease in the western world, can be categorized as either ''high pressure'' or ''normal pressure'', depending whether the IOP lies above or under the normally expected range, In both cases, there is a characteristic cupping of the optic disc along with possible visual field loss and loss of retinal ganglion cells. If the IOP is consistently more than two standard deviations above the normal mean, while all other ocular findings (visual field, optic disc appearance etc.) are within normal limits, the condition is classified as ocular hypertension (OH). Exfoliation syndrome and pigment dispersion are risk factors for secondary open-angle glaucoma. Trauma, or conditions such as uveitis, may cause damage to the drainage pathways within the eye, and, therefore, be linked to the onset of secondary open-angle glaucoma (Yee, 2007).

Angle-closure glaucoma (AGC), is caused by forces which either pull (e.g., neovascularization of the iris, inflammation) or push (pupillary block, posterior synechiae, uveitis) the iris forward or push the lens forward (e.g., mature cataract, small anterior segment) thereby narrowing the iridocorneal angle. In its primary form, angle closure is more frequent in Asian population.

Although many molecules aimed to arrest or even reverse the apoptotic damage of the optic nerve and retinal ganglion cells (Ammar et al., 2011), elevated IOP is still considered the most important risk factor for glaucoma development. At present, the only effective treatment for glaucoma is to lower the IOP and for this purpose a broad spectrum of medications are available (Leske et al., 2008).

IOP can be lowered either through a decrease of aqueous production (i.e., the amount of aqueous that is produced by the ciliary tissues), or by increasing outflow through the conventional trabecular pathway or the alternate uveoscleral pathway.

Many of the currently available topical medications are associated with adverse effects, such as dry eye, burning, stinging sensations, tearing and allergic reactions (Jaenen et al., 2007). Discomfort due to instillation, or ocular adverse events caused by the drug itself, may have an impact on the patient's quality of life, and are thought to be associated with poor compliance. This leads to poor IOP control, which in turn, may increase the need for eventual filtration surgery, which is associated with risks, the most common being an increase cataract formation (Baudouin, 2008).

2. Antiglaucoma drugs and therapeutic regimens

The goal of glaucoma treatment is to maintain the patient's visual function and related quality of life (European Glaucoma Society, 2008b). Besides the functional loss and having the diagnosis of a potentially blinding disease, other factors alone or in combination may affect patients' quality of life: inconvenience of the treatment, side effects and therapy costs.

Most patients with POAG are initially treated with topical medications. Ideally one should use the lowest dose of a particular drug that will produce the greatest therapeutic response with the least number of side effects. Indeed, many of the currently available topical medications are associated with adverse effects, such as dry eye, burning, stinging sensations, tearing and allergic reactions (Jaenen et al., 2007). There is a general consensus to start glaucoma medical therapy with one topical intraocular pressure (IOP) lowering medication. If the first choice monotherapy alone is not effective to reduce IOP or is not tolerated, it is preferable to switch to another molecule that is initiated as monotherapy. Adjunctive therapy should be considered whenever a monotherapy does not reach target IOP or the target must be lowered as the disease is progressing (South East Asia Glaucoma Interest Group, 2008; European Glaucoma Society, 2008c). Antiglaucoma drugs can be combined with each other in order to reach the target IOP. As a general rule, in most patients it is not recommended to use more than two drugs in two separate bottles or to add more than one single drug to a fixed-combination since compliance is likely to suffer. However, multiple topical treatments are often required to reduce the IOP to the desirable target.

Glaucomatous patients have been shown to suffer from symptoms related to ocular surface disease (i.e., burning, itching, red eye, tearing, blurred vision) in a higher prevalence than normal population (Stewart et al., 2011). Although the cause is

thought to be multi-factorial, the chronic use of topical medications seems to play a major role and the prevalence appears to increase with the greater the number of antiglaucoma drops prescribed (Stewart et al., 2011). Long-term use of topical drugs, especially in those patients receiving a multiple drop regimen, may be detrimental as a dose- and time-dependent consequence to benzalkonium chloride exposure (Serle et al., 2004) There is now increasing evidence to demonstrate that a sizable portion of local side effects may result from the preservatives rather than from the active compounds. There may be a direct correlation between the presence of preservatives and the surface symptoms provoked by anti-glaucoma therapy (Serle et al., 2004); reducing such exposure could improve the patient's comfort and thus his compliance.

3. Antiglaucoma drugs and allergic reactions

Topical IOP-lowering drugs can cause different reactions on ocular structures, especially on the ocular surface. Proper allergic reactions can be clinically serious, however, their incidence is definitely lower than the non-allergic alterations caused by the chronic use of such drugs. The incidence of proper allergic reactions is very different, depending on the compound. Immediate allergic reactions are less frequent with timolol than with other hypotensive drugs (Osborne et al., 2005).

Some authors reported an incidence of 1.5% of allergic reactions with latanoprost, when used as a second-line therapy (Haverkamp et al., 2004).

Allergic reactions with brimonidine have been reported to be between 4.2% and 25.7% (Manni et al., 2004); a lower incidence has been reported with the use of the fixed combination brimonidine-timolol (Manni et al., 2004; Motolko, 2008).

Severe periocular dermatitis, possibly associated with atypical likenoid reactions was reported to be associated with the use of dorzolamide, even months after the beginning of the therapy; the incidence of this type IV hypersensitivity reactions are over all quite uncommon (Mullins et al., 2004; Delaney et al., 2002).

4. Antiglaucoma drugs and ocular surface

Several epidemiological studies demonstrated that patients on local IOP-lowering therapies complained about local discomfort (Jaenen et al., 2007; Pisella et al., 2002). The occurrence of ocular surface disease (OSD) may be related to different factors, such as age, sex, race, the presence of blepharitis and the use of preserved eye drops (Brewitt and Sistani, 2001; Baudouin and de Lunardo, 1998; Leung et al., 2008). Besides the allergic reactions caused by the active compounds, preservatives contained in the preparations may trigger an inflammatory response. As with all patients affected by OSD, signs and symptoms are not always related and many glaucomatous patients that complain of dry eye symptoms do not have any measurable damage and vice-versa (Hay et al., 1998); however, the discomfort related to antiglaucoma eyedrops use has been reported as one of the most common causes of request for an ophthalmological consultation. The symptoms may be related either to the instillation or to the period between different instillations. Stinging and burning are common just after the instillation of the eye-drops. Up to 25% of patients complain the occurrence of side effects such as "pain" immediately after the beginning of the therapy. The percentage rises up to 40% if the symptom sought for is "burning" that might also cause tearing. Other common symptoms are dry-eye sensation and itching of the palpebral margin. Conjunctival hyperemia related to topical prostaglandin application is usually considered disagreeable by the patient. It is caused by a local vasodilatation and its gravity is related to the compound and to individual reactivity (Hollò, 2007). Usually the degree of hyperemia is apparently more severe than the symptoms (burning, stinging and itching).

Glaucoma patients are at high risk for developing ocular surface disease because:

- Both glaucoma and OSD incidence increases with the age.
- A large portion of glaucomatous patients are treated with preservative-containing pressure lowering eyedrops.
- The treatment is usually prolonged for years since glaucoma is a chronic disease.

Besides OSD related discomfort and anatomical alterations, several authors found a correlation between chronic topical long-term therapy and a higher rate of subsequent filtration surgery failure (Leung et al., 2008; Broadway et al., 1994; Yee, 2007). Immediately after surgery fibroblasts tend to proliferate, in order to repair the incised tissues, thus reducing the filtration of aqueous humor to the subconjunctival space. An increase in inflammatory response leads to faster recruitment of fibroblasts that produce extracellular matrix. Long-term therapy with preserved local hypotensive drugs leads to conjunctival migration of macrophages and lymphocytes.

The conjunctival inflammatory reaction in glaucomatous patients seems to be related both to the number of eye-drops instillation and to the duration of the therapy. The toxic effect of preservatives is likely to play a relevant role in the conjunctival cicatricial response after surgery (Baudouin, 1996, 2008).

5. Antiglaucoma drugs and preservatives

There is increasing evidence to demonstrate that a sizeable portion of local side-effects may result from the preservatives rather than from the active compounds. The most commonly used preservative in anti-glaucoma medications is benzalkonium chloride (BAK). BAK has been shown (Baudouin et al., 1999) to induce significant inflammatory and histopathological changes in both the ocular surface and deeper ocular structures, and to induce apoptosis in conjunctival cells (Debbasch et al., 2001).

As a quaternary ammonium, BAK, is most commonly associated with irritant toxic reactions (8% in OVID and PubMED based researches), whereas the organomercurials, such as thimerosal, and the alcohols, such as chlorobutanol, have the highest associations with allergic responses (respectively, 19% of OVID and 14% of PubMED based researches and 20% of OVID and 11% of PubMED based researches). Such reactions appear mainly like an irritant effect for alcohols, whereas the organo-mercurials appear to truly interact with the immune system as neoantigens (Hong and Bielory, 2009). Non-quaternary ammonium preservatives seem to cause oxidative stress to a significantly lesser extent and to induce lower cell death rate than BAK (Debbash et al., 2001).

The mechanism causing tear film instability, loss of globlet cells, conjunctival squamous metaplasia and apoptosis, disruption of the corneal epithelium barrier and damage of deep ocular tissues are far from being fully elucidated, but the involvement of immunoinflammatory reactions was proposed. The release of proinflammatory cytokines, apoptosis, oxidative stress as well as direct interactions with the lipid layer of the tear film and cell membranes are well established (Baudouin et al., 2010).

6. Antiglaucoma drugs: how to reduce the exposure to preservatives?

Despite consistent data confirming its potential toxic effects, especially for a chronic use, BAK is still used as the main preservative in eye drops. Considerable efforts have been made by the pharmaceutical industry in the recent past, however, to develop new antiglaucoma formulations that would bring about efficacy, safety and compliance. The most part of the antiglaucoma drugs that have been commercialized during the last years allows for a lower BAK exposure.

Different strategies can be considered in order to reduce the amount of BAK administered when prescribing a therapeutic antiglaucoma regimen.

6.1. Reducing the number of drops

As BAK toxicity is mainly dose-dependent, reducing the number of instillations can improve ocular tolerance (Baudouin et al., 2010).

Prostaglandins and long-acting preparations of timolol are given once rather than twice a day, thus reducing the amount of BAK administered by 50% (Easty et al., 2006).

The same occurs with the use of fixed-combined drugs preparations. Fixed combinations of timolol and prostaglandins, carbonic anhydrase inhibitors and brimonidine are currently on the market and represent an important tool in order to optimize glaucoma therapy. When two or more active molecules are necessary to obtain an adequate IOP, fixed-dose combination eye drops may offer advantages for patients, while maintaining at least the same effect on IOP than separate instillation of the same two products (European Glaucoma Society, 2008c). As a general rule, compliance with any given medical therapy in glaucoma, like other chronic diseases, is better when regimens are simple rather than complex and reducing the number of daily administrations can positively affect patients' quality of life (Olthoff et al., 2005). Moreover, the higher costs from more bottles seem to promote non-compliance and reduce persistence (Soumerai et al., 2006). Besides possible improved compliance, quality of life, costs saving and also additional IOP lowering effect for some molecules (Higginbothan, 2010), fixed combinations allow for halving the daily amount of BAK and related side-effects. Although no definitive data exist, at least some of the currently available fixed combination have shown a better safety profile and tolerability when compared with the same molecules used separately (Sleath et al., 2006; Hommer, 2007).

6.2. Using of preserved formulation not containing BAK

Overall, BAK has an apparently good safety/efficacy profile; it is weakly allergenic and has a high rate of antimicrobial properties. Worth to remember is that the Pharmacopoeia recommends that eye drops must contain an antimicrobial agent (preservative) to avoid or limit microbial proliferation after opening of the bottle, which could induce a risk of potentially severe eye infection as well as alteration of the formulation (Baudouin et al., 2010). Conversely, definitive data suggest that avoiding its toxicity should be of benefit for a large portion of glaucomatous patients. Extensive research has been conducted to discover and develop less toxic preservatives than quaternary ammoniums. However, since preservatives must be potent antimicrobial agents while not being cytotoxic, only few agents have been proposed and are commercially available (Baudouin et al., 2010). Purite® is a stabilized oxychloro complex acting as an oxidative preservative that is converted into natural tear components when exposed to light (Kim et al., 2007). This molecule has shown a wide spectrum of antimicrobial activity and a very low-level toxicity in mammalian cells (Grant et al., 1996). When Purite® was used in formulations of brimonidine 0.15% it resulted in significantly better tolerance as compared to BAK containing brimonidine 0.2%, especially in irritated eyes (Mundorf et al., 2003). Sofzia® is a preservative system composed of boric acid, propylene glycol, sorbitol and zinc chloride that causes oxidative damage and consequent death to organisms that lack the enzymes cytochrome oxidase and catalase, such as most species of bacteria; human cells posses these enzymes and are thus not similarly harmed (Ammar et al., 2010). Henry and coworkers found significant improvement of ocular surface symptoms and hyperemia and similar IOP lowering effect when patients treated with latanoprost or bimatoprost were switched to Sofzia-preserved travoprost (Henry et al., 2008). Polyquad (polyquaternium-1) belongs to the family of plycationic polymers named polyquaternium and is commonly used as a multi-

Table 1 Summary of the antiglaucoma drugs currently available in either preservative- and/or BAK-free formulations.

Category	Molecule	Pharmaceutical form
β-Blockers	Timolol 0.5–0.1%	Single dose container/ABAK®, COMOD® system
	Betaxolol 0.25%	Single dose container
	Levobunol 0.5%	Single dose container
	Carteolol 1–2%	Single dose container/ABAK® system
Carbonic anhydrase inhibitors	Dorzolamide 2%	Single dose container
α-Agonists	Brimonidine 0.1–0.15%	BAK-free solution (preservative: Purite®)
Prostaglandin analogues/prostamides	Tafluprost 0.0015%	Single dose container
	Travoprost 0.004%	BAK-free solution (preservative: Sofzia®, Polyquad)
Parasympathomimetics	Pilocarpine	Single dose container
Fixed combinations:	Timolol-Dorzolamide	Single dose container

purpose solution for contact lenses and is currently used in eye drops as an alternative to BAK (Lipener, 2009). Labbe et al showed higher toxic effects in the ocular surface of rats treated with BAK than those exposed to Polyquad (Labbe et al., 2006). Similarly, Ammar et al found that the substitution of BAK with Polyquad resulted in significantly higher percentages of human live conjunctival and corneal cells (Ammar et al., 2011).

6.3. Preservative-free formulations

The only way to completely eliminate BAK/preservative-related side effects is obviously to remove them from the eyedrops. However, due to the above mentioned Pharmacopoeia recommendations, this approach raises industrial and regulatory concerns since non-preserved eyedrops in multidose bottles could enhance the risk of contamination.

To address this concern, single-dose units are the most frequently used preservative-free formulations. Different beta-blockers, pilocarpine and more recently a fixed combination of timolol and dorzolamide as well as the prostaglandin analogue tafluprost have been commercialized as single-dose units (Hommer and Kimmich, 2011). Less cost-effectiveness and difficult handling have been pointed out regarding these formulations and their use by older patients and with inappropriate finger manipulation could be associated with an increased risk of contamination. However, Kim et al reported that even in the worst conditions of poor administering technique of unpreserved artificial tears, only 2% of 242 reclosable containers had bacterial contamination after three times or more instillation within 10 h (Kim et al., 2008). Conversely, Tasli and Cosar found a 35% rate of contamination after 15 days in a multiple-use setting of bottles preserved with BAK (Tasli and Cosar, 2001).

Newer multidose formulations have been developed: either by allowing for preservative filtration and adsorption on a porous membrane or by using a valve system that hinders penetration of bacteria into the bottle (Baudouin et al., 2010). Different beta-blockers have been available with the ABAK® or COMOD® systems for a number of years. Different clinical studies confirmed substantial improvement of the patient's ocular surface after starting the use of BAK-free drops (Baudouin et al., 2010).

7. Conclusions

When selecting medical treatment for glaucoma it is important to understand not only the primary aim of the therapy but also contraindications and side effects of each medication for every single patient. Besides efficacy, the choice of therapy must take into account tolerability, related quality of life and adherence to treatment (European Glaucoma Society, 2008c). Preservatives contained within topical eye drop preparations may cause inflammatory conjunctival side effects and toxicity of the ocular surface (Blondin et al., 2003; Baratz et al., 2006).

The use of preservative-free preparations/delivery systems, the reduction of the number of instillation or the choice of formulations containing preservatives less toxic than BAK should be considered to lessen such problems. This should lead to better tolerability and possibly higher adherence to the treatment and improvement of patients' quality of life.

Within the past 5–7 years, a number of ocular hypotensive drugs have been re-formulated in preservative-free versions and some have changed preservatives, while maintaining equally effective IOP-lowering effects. Preservative free formulations of timolol, betaxolol, dorzolamide, a fixed combination of timolol-dorzolamide and tafluprost are actually available; formulations of travoprost and brimonidine containing preservatives less toxic than BAK are also available (see Table 1).

As a general rule, preservative-free eyedrops could be particularly beneficial to patients with the following characteristics (Baudouin, 2008; Bagnis et al., 2011; European Glaucoma Society, 2008a,b,c):

- pre-existing or concomitant dry eye/ocular surface disease
- those receiving a multidrug topical treatment
- those whose treatments are expected to last over several years/decades
- those who are about to undergo glaucoma surgery.

Patients showing one or more of these features are likely to benefit from BAK-free formulations as well as from minimizing the exposure to BAK by the use of fixed combined preparations.

References

Ammar, D.A., Noecker, R.J., Kahook, M.Y., 2010. Effects of benzalkoium chloride-preserved, polyquad-preserved, and Sofzia-preserved topical glaucoma medications on human ocular epithelial cells. Adv. Ther. 27, 837–845.

Ammar, D.A., Noecker, R.J., Kahook, M.Y., 2011. Effects of benzalkonium chloride- and polyquad-preserved combination glaucoma medications on cultured human ocular surface cells. Adv. Ther. 28, 501–510.

Bagnis, A., Papadia, M., Scotto, R., Traverso, C.E., 2011. Current and emerging medical therapies in the treatment of glaucoma. Expert Opin. Emerging Drugs 16, 293–307.

Baratz, K.H., Nau, C.B., Winter, E.J., McLaren, J.W., Hodge, D.O., Herman, D.C., Bourne, W.M., 2006. Effects of glaucoma medications on corneal endothelium, keratocites and subbasal nerves among participants in the ocular hypertension treatment study. Cornea 25, 1046–1052.

Baudouin, C., 1996. Side effects of antiglaucomtaous drugs on the ocular surface. Curr. Opin. Ophthalmol. 7, 80–86.

Baudouin, C., 2008. Detrimental effect of preservatives in eyedrops: implications for the treatment of glaucoma. Acta Ophthalmol. 86 (7), 716–726.

Baudouin, C., de Lunardo, C., 1998. Short-term comparative study of topical 2% carteolol with and without benzalkonium chloride in healthy volunteers. Br. J. Ophthalmol. 82, 39–42.

Baudouin, C., Pisella, P.J., Goldschild, M., et al., 1999. Ocular surface inflammatory changes induced by topical antiglaucoma drugs: human and animal studies. Ophthalmology 105, 556-556.

Baudouin, C., Labbé, A., Liang, H., Pauly, A., Brignole-Baudouin, F., 2010. Preservatives in eyedrops: the good, the bad and the ugly. Prog. Retin. Eye Res. 29 (4), 312–334, Epub 2010 Mar 17.

Blondin, C., Hamard, P., Cholley, P., Haeffner_Cavaillon, N., Baudouin, C., 2003. In vitro effects of preserved or preservative-free antiglaucoma medications on human complement system. Curr. Eye Res. 27, 253–259.

Brewitt, H., Sistani, F., 2001. Dry eye disease: the scale of the problem. Surv. Ophthalmol. 45, 199–202.

Broadway, D.C., Griersin, I., O'Brien, C., Hitchings, R.A., 1994. Adverse effects of topical antiglaucomatous medications, II: The out come of filtration surgery. Arch. Ophthalmol. 112, 1446–1454.

Coleman, A.L., 1999. Glaucoma. Lancet 354 (9192), 1803–1810.
Debbasch, C., Brignole, F., Pisella, P.J., 2001. Preservatives contribution in oxidative stress and apoptosis on Chang conjunctival cells. Invest. Ophthalmol. Vis. Sci. 42, 642–652.
Debbash, C., Pisella, P.J., De Saint Jean, M., Rat, P., Warnet, J.M., Baudoin, C., 2001. Mitochondrial activity and glutathione injury in apoptosis induced by un preserved and preserved beta-blockers on Chang conjunctival cells. Invest. Ophthalmol. Vis. Sci. 42, 2525–2533.
Delaney, Y.M., Salmon, J.F., Mossa, F., Gee, B., Beehne, K., Powell, S., 2002. Periorbital dermatitis as a side effect of topical dorzolamide. Br. J. Ophthalmol. 86, 378–380.
South East Asia Glaucoma Interest Group. Medical treatment. In: Asia Pacific Glaucoma Guidelines (2nd ed.), SE AGIG, Sydney, Australia; 2008. p. 25–28.
Easty, D.L., Nemeth-Wasmer, G., Vounatsos, J.-P., Girard, B., Besnainou, N., Pouliquen, P., Delval, L., Rouland, J.-F., 2006. Comparison of a non-preerved 0.1% T-Gel eye gel (single dose unit) with a preserved 0.1% T-Gel eye gel (multidose) in ocular hypertension and glaucomatous. Br. J. Ophthalmol. 90, 574–578.
European Glaucoma Society. Classification and terminology. In: Heijl A, Traverso CE, editors, Terminology and guidelines for glaucoma. 3rd edition. Savona, Dogma s.r.l.; 2008. p. 95-7 (a).
European Glaucoma Society Treatment principles and options. Terminology and Guidelines for Glaucoma (3rd ed.), DOGMA Srl, Savona, Italy; 2008. p. 117 (b).
European Glaucoma Society. Treatment principles and options. In: Heijl A, Traverso CE, editors, Terminology and guidelines for glaucoma. 3rd edition. Savona, Dogma s.r.l.; 2008. p. 122-126 (c).
Falkenberg, H.K., Bex, P.J., 2007. Sources of motion-sensitivity loss in glaucoma. Invest. Ophthalmol. Vis. Sci. 16 (6), 2913–2921.
Grant, R., Ajello, M., Vlass, E., 1996. Salt water or high tech? a look at new rinsing solutions for contact lenses. Optician 212, 38–41.
Haverkamp, F., Wuensch, S., Fuchs, M., Stewart, W.C., 2004. Intraocular pressure, safety and quality of life in glaucoma patients switching to latanoprost from adjunctive and monotherapy treatments. Eur. J. Ophthalmol. 14, 407–415.
Hay, E.M., Thomas, E., Pal, B., et al., 1998. Weak association between subjective symptoms or and objective testing for dry eyes and dry mouth: results from a population based study. Ann. Rheum. Dis. 57, 20–24.
Henry, J.C., Peace, J.H., Stewart, J.A., Stewart, W.C., 2008. Efficacy, safety and improved tolerability of travoprost BAK-free ophthalmic solution compared with prior prostaglandin therapy. Clin. Ophthalmol. 2, 613–621.
Higginbothan, E.J., 2010. Considerations in glaucoma therapy: fixed combinations vs their component medications. Clin. Ophthalmol. 4, 1–9.
Hollò, G., 2007. The side effects of the prostaglandin analogues. Expert Opin. Drug Saf. 6, 45–52.
Hommer, A., 2007. A double-masked, randomized, parallel comparison of a fixed combination of bimatoprost 0 03%/timolol 0.5% with non-fixed combination use in patients with glaucoma or ocular hypertension.. Eur. J. Ophthalmol. 17, 53–62.
Hommer, A., Kimmich, F., 2011. Switching patients from preserved prostaglandin-analog monotherapy to preservative-free tafluprost. Clin. Ophthalmol. 5, 623–631.
Hong, J., Bielory, L., 2009. Allergy to ophthalmic preservatives. Curr. Opin. Allergy Clin. Immunol. 9 (5), 447–453.
Jaenen, N., Baudouin, C., Poliquen, P., et al., 2007. Ocular symptoms and signs with preserved and preservative-free glaucoma medications. Eur. J. Ophthalmol. 17, 341–349.
Kim, C.Y., Hong, S., Seong, G.J.E., 2007. Brimonidine 0.2% vs Brimonidine Purite 0.15% in asina ocular hypertension.. J. Ocul. Pharmacol. Ther. 23, 481–486.
Kim, M.S., Choi, C.Y., Kim, J.M., Chang, H.R., Woo, H.Y., 2008. Microbial contamination of multiply used preservative-free artificial tears packed in reclosable containers. Br. J. Ophthalmol. 92, 1518–1521.
Labbe, A., Pauly, A., liang, H., Brignole-Baudoin, F., Martin, C., Warnet, J.M., Baudoin, C., 2006. Comparison of toxicological profiles of benzalkonium chloride and polyquaternium-1: an experimental study. J. Ocul. Pharmacol. Ther. 22, 267–278.
Leske, M.C., Wu, S.Y., Hennis, A., et al.ESs Study Group, 2008. Risk factors for incident open-angle glaucoma: the Barbados Eye Studies. Ophthalmology 115 (1), 85–93.
Leung, E.W., Medeiros, F.A., Weinreb, R.N., 2008. Prevalence of ocular surface disease in glaucoma patients. J. Glaucoma 17 (5), 350–355.
Lipener, C., 2009. A randomized clinical comparison of OPTI-FREE EXPRESS and ReNu MultiPlus multipurpose lens care solutions. Adv. Ther. 26, 435–446.
Manni, G., Centofanti, M., Sacchetti, M., et al., 2004. Demographic and clinical factors associated with the development of brimonidine tartrate 0. 2%-induced ocular allergy. J. Glauc. 13 (2), 163–167.
Motolko, M.A., 2008. Comparison of allergy rates in glaucoma patients receiving brimonidine 0.2% monotherapy versus fixed-combination brimonidine 0.2%-timolol 0.5% therapy. Curr. Med. Res. Opin. 24 (9), 2663–2667.
Mullins, R.J., Lones, R., Dutta, B., 2004. Lichenoid drug eruption secondary to topical timolol and dorzolamide eye-drops. Australas J. Dermatol. 45, 151–152.
Mundorf, T., Wilcox, K.A., Ousler, G.W., Welch, D., Abelson, M.B., 2003. Evaluation of the comfort of Alphagan P compared with Alphagan in irritated eyes. Adv. Ther. 20, 329–336.
Olthoff, C.M., Schouten, J.S., Van de Brne, B.W., Webers, C.A., 2005. Non compliance with ocular hypothensive treatment in patients with glaucoma or ocular hypertension: an evidence-based review. Ophthalmology 112 (6), 953–961.
Osborne, S.A., Montgomery, D.M., Morris, D., et al., 2005. Alphagan allergy may increase the propensity for multiple eye-drop allergy. Eye 19 (2), 129–137.
Pisella, P.J., Pouliquen, P., Baudouin, C., 2002. Prevalence of ocular symptoms and signs with preserved and preservative-free glaucoma medication. Br. J. Ophthalmol. 86, 418–423.
Serle J, Toor A, Fahim M, et al. The effect of varying dosing intervals on the efficacy of intraocular pressure lowering drugs. Invest. Ophthalmol. Vis. Sci. 2004;45: ARVO E-Abstract 974.
Sleath, B., Robin, A.L., Covert, D., et al., 2006. Patient-reported behavior and problems in using glaucoma medications. Ophthalmology 113, 431–436.
Soumerai, S.B., Pierre-Jacques, M., Zhang, F., et al., 2006. Cost-related medication nonadherence among elderly and disabled Medicare beneficiaries: a national survey 1 year before the Medicare drug benefit. Arch. Intern. Med. 166, 1829–1835.
Stewart, W.C., Stewart, J.A., Nelson, L.A., 2011. Ocular surface disease in patients with ocular hypertension and glaucoma. Curr. Eye Res. 36, 391–398.
Tasli, H., Cosar, G., 2001. Microbial contamination of eye drops. Eur. J. Public Health 9, 162–164.
Yee, R.W., 2007. The effect of drop vehicle on the efficacy and side effects of topical glaucoma therapy: a review. Curr. Opin. Ophthalmol. 18, 134–139.