TAFLOTAN®, THE FIRST PRESERVATIVE-FREE PROSTAGLANDIN F2α ANALOGUE: TREATMENT ADVANTAGES IN PRIMARY OPEN-ANGLE GLAUCOMA PATIENTS

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Over the past 15 years, the negative role of toxic preservatives in the IOP-lowering eye drops solutions used in the treatment of primary open angle glaucoma (POAG) patients has been convincingly proven by many national and foreign experts. Therefore, there is a worldwide tendency to prescribe preferably preservative-free IOP-lowering eye drops nowadays. Taflotan is the world’s first preservative-free prostaglandin F2α analogue. In our study of POAG patients switched to Taflotan from the benzalkonium chloride-preserved latanoprost eye drops, we observed a marked decrease in corneal staining and severity of conjunctival hyperemia, as well as an increase of the tear breakup time and corneal epithelium morphology improvement evaluated by confocal tomography. Thus, the drug not only effectively lowers IOP but also produces less negative effect on the tear film and eyeball surface, improving treatment tolerability.

Key words: glaucoma; tafluprost; benzalkonium chloride; confocal tomography, cornea.

Glaucoma is a leading cause of irreversible blindness in the world. Its effective treatment is of high priority for modern ophthalmology. Currently, 1.3 million patients with glaucoma are officially registered in the Russian Federation, with the number continuously growing. Despite the latest achievements in research and practice, the main methods for glaucoma treatment are medical therapy, laser treatment, and various surgical procedures. About 60%—80% of patients undergo medicamentous therapy in the form of IOP-
lowering drops instillation. Lack of awareness in patients regarding the steadily progressive nature of the disease, a casual attitude to treatment, and the development of side effects of a local therapy often result in patient noncompliance with the recommended instillation regimen. According to data from European and domestic ophthalmologists, 40%–65% of patients irregularly instill their antihypertensive drugs, with treatment compliance significantly decreasing as the number of instillations per day increases [1, 31]. Up to 30% of patients discontinue treatment because of various side effects, and this leads to further progression of glaucoma atrophy and to gradual irreversible loss of visual function. Therefore, numerous long-term studies in the field of local antihypertensive therapy have focused their research on a drug that would be not only effective but also safe and having a convenient dosage regimen.

Prostaglandin F2α analogs, which first appeared in the market in 1996, have recently become the indisputable leaders among antihypertensive drops. Their action mechanism (improvement of uveoscleral outflow) essentially differs from that of pilocarpine and timolol, which are the drugs traditionally used in the past. Prostaglandin F2α analogs allow the attainment of the maximum possible antihypertensive effect for monotherapy with a once daily instillation regimen.

The medications based on this concept are currently recognized as “the gold standard” of therapy for patients with primary open-angle glaucoma (POAG). The lack of systemic side effects and the relatively small number of local side effects are important advantages. However, their use is limited to patients with uveal glaucoma who have concomitant macular edema. The advisability of administering prostaglandin analogs to patients with compensated diabetic retinopathy or with forthcoming cataract surgery has not been clearly refuted.

The main local side effect of prostaglandin analogs is conjunctival hyperemia, which typically causes the main cosmetic problem of “red eyes” and which may become a reason for therapy interruption. Hyperemia onset is associated with two factors: the effect of the main active agent on conjunctival vessels and the harmful effect of preservative on the surface structure of the eyeball and tear film. According to accumulated data, the development rate of conjunctival hyperemia and its intensity differ with respect to prostaglandin drugs (Fig. 1).

Over the last 15 years, adverse effects of preservatives have been intensively studied. Numerous experimental and clinical studies have conclusively demonstrated the negative effect of preservative on tear film, cornea, conjunctiva, and even trabecular meshwork [6, 7, 11, 16, 23, 30, 37]. This is not surprising, as many preservatives have properties similar to those of surface-active compounds and detergents, which can damage the lipid layer of the tear film. In addition, they can produce a cytotoxic effect on human epithelial cells. The mechanism of such changes is inherent in the nature of the preservatives. Their selection has always been based on obtaining the

**Fig. 1.** Comparative characteristics of conjunctival hyperemia intensity associated with the use of different prostaglandin analogs
maximum possible antibacterial effect with minimal toxic and allergic reaction. Thus, for example, the use of thiomersal was eventually discontinued because of its apparent toxic effect.

In 1966, benzalkonium chloride (BAC) was proposed for use in ophthalmic drugs. At the time, it seemed to be the best alternative as it had a wide spectrum of antibacterial activity and a relatively low incidence of allergic reaction development [7]. Thanks to these properties, BAC quite quickly became the most common preservative in ophthalmology, and it remains a component of the majority of eye drops. Its antibacterial effect is substantial; it not only inhibits a great part of gram-positive flora but also exhibits fungicidal activity even in low concentrations. In experimental studies, BAC retained sterility longer than other ophthalmic solutions [12, 35], showing its efficacy as a preservative. Its presence in the composition of anti-infective drugs improves the efficiency of antibacterial therapy, and the toxic effect on the corneal epithelium improves the penetration of the drugs into the deeper layers of the cornea and into the anterior chamber fluid, improving the efficiency of treatment of bacterial keratitis and other conditions. However, these properties of BAC are only beneficial with short-term use of the drug. During continuous use of eye drops that contain BAC, its regular action on the tear film and superficial epithelium causes a range of long-term adverse changes. Among these, the continuous destruction of the lipid layer of the tear film leads to an increase in evaporation; the cytotoxic effect of BAC on the conjunctival epithelial cells and goblet cells reduces their number [7]. This leads to a deficiency of lactate, pyruvate, mucins, and other important components of the tear film, causing the development or aggravation of the course of dry eye syndrome (DES). With this, BAC tends to accumulate in epithelial cells, increasing its toxic effect [7]. The long-term cytotoxic effect of BAC on the conjunctival and corneal epithelium includes changes in the normal function and activity of cells, with time triggering their death through apoptosis [14]. These changes were reported for the standard concentration of preservative (0.01 % and above); at concentrations less than 0.005 %, BAC does not cause cell death but slows down mitosis [7, 13]. Switching to an IOP-lowering drug without a preservative not only improves tear film stability and corneal epithelium state, but also results in an increase in the number of goblet cells [9, 17, 25, 27, 36].

The chronic effect of toxic preservatives induces so-called proinflammatory conjunctiva readiness with a rise in the concentration of cytokines, which are inflammatory mediators [7–9, 19]. Later, this may become a reason for the decline in the efficacy of surgical procedures, enhancing the scarring in the filtration zone of the conjunctiva. According to the data of Broadway et al., the success of IOP-lowering surgeries declined from 90 % to 45 % in patients who previously received long-term drug therapy with a preservative [10].

Through a mediated antioxidative effect, prostaglandin analogs can reduce BAC toxicity in comparison with IOP-lowering drops from other pharmacological classes [18, 21, 37]. The prescription of “artificial tears” with hyaluronic acid reduces by half the toxicity of BAC on surface epithelial cells [7].

Thus, DES manifestations can be found in most glaucoma patients [5, 15, 20, 24]. In routine clinical practice, it is hard to distinguish between the signs of cytotoxic reaction and DES, that is why a study was undertaken in our clinic involving a detailed assessment of the state of the corneal epithelium using confocal tomography (Confoscan 4, Nidek, Japan). This study included 70 glaucoma patients who received IOP-lowering drug treatment with a preservative for more than 3 months. The comparison group included 70 patients of the same age group with DES but without glaucoma and without any local therapy. The obtained results are presented in Table 1.

Excessive desquamation of corneal superficial epithelial cells primarily was a manifestation of DES (Fig. 2, b); this was found in the great majority of participants in both groups (see Table 1). However, the severity was greater in the glaucoma group, which can be explained by the impairment of epithelium barrier function due to the destruction of intercellular junctions caused by the IOP-lowering drop preservative (i.e., BAC).

The distortion of row order and morphology of corneal superficial epithelial cells, edema extending to the basal epithelium and superficial stroma occurred far less often in the comparison group ($p < 0.001$). The intensity of anterior stromal edema was higher in the glaucoma patient group (Fig. 5) who received drug therapy with BAC, which also indicates impairment of the barrier function of the corneal epithelium in the patient group and results from a disturbance in stromal fluid balance. The changes in corneal epithelial cell morphology (their shape, size, borders, and nucleus–cytoplasm ratio) found in glaucoma patients who took IOP-lowering drops with preservative were virtually absent in the comparison group (see Table 1). These signs can be associated with the immediate cytotoxic action of the preservative contained in IOP-lowering drops as there was found to
Comparative analysis of corneal changes in patients with primary open-angle glaucoma (POAG), who received medicamentous therapy, and patients with dry eye syndrome (DES), who did not receive any therapy

<table>
<thead>
<tr>
<th>Assessment parameter of confocal cornea tomograms</th>
<th>Patients with POAG who received IOP-lowering drops with preservative</th>
<th>Patients with DES without glaucoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excessive desquamation of superficial epithelial cells</td>
<td>69 (98.6 %)</td>
<td>69 (98.6 %)</td>
</tr>
<tr>
<td>Breakdown of surface epithelial cells</td>
<td>56 (80 %)</td>
<td>42 (60 %)</td>
</tr>
<tr>
<td>Distortion of superficial cell morphology and corneal epithelium row order</td>
<td>39 (57.7 %)</td>
<td>2 (2.9 %)</td>
</tr>
<tr>
<td>Change in basal epithelium</td>
<td>57 (81.4 %)</td>
<td>17 (24.3 %)</td>
</tr>
<tr>
<td>Change in superficial nerve filaments</td>
<td>56 (80 %)</td>
<td>26 (37.1 %)</td>
</tr>
<tr>
<td>Edema of superficial layers of the corneal stroma</td>
<td>69 (98.6 %)</td>
<td>56 (80 %)</td>
</tr>
<tr>
<td>Activation of stromal keratocytes</td>
<td>67 (95.7 %)</td>
<td>56 (80 %)</td>
</tr>
<tr>
<td>Intrastromal fine inclusions</td>
<td>33 (47.1 %)</td>
<td>9 (12.9 %)</td>
</tr>
<tr>
<td>Changes in the posterior corneal epithelium</td>
<td>45 (64.3 %)</td>
<td>40 (57.1 %)</td>
</tr>
</tbody>
</table>

be a significant dependence of the changes on the duration and regimen of previous medical therapy ($p < 0.001$). In the glaucoma patients who took two or more antihypertensive drugs simultaneously for longer than 6 months, pronounced changes were found in all the corneal structures studied.

The depletion of subepithelial nerve plexus with thinning and increased coiling of nerve filaments (Fig. 3) found in glaucoma patients who received medicamentous treatment deserves special attention. In the comparison group, the changes were found in far fewer cases and mainly in older patients ($p < 0.001$). In addition, the changes of superficial nerve endings in the comparison group manifested as general depletion of the nerve filament pattern, whereas in the main group the nerve endings were sharply and unevenly thinned and strongly coiled. The changes were ascribed as being manifestations of the toxic effect of preservative and were more pronounced in glaucoma patients who received medical treatment for longer than 3 years [6, 16, 26].

The intrastromal fine inclusions (Fig. 4) found in patients with POAG could be regarded as a manifestation of degenerative processes in the corneal stoma, as in the comparison group they occurred only in patients older than 70 ($p < 0.001$). Apparently, earlier

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**Table 1**

**Fig. 2.** Excessive desquamation of the corneal superficial epithelial cells ($a$, $b$) with early morphology changes ($a$) in a patient with primary open-angle glaucoma who received IOP-lowering drops with benzalkonium chloride ($a$) and in a patient with DES ($b$)
onset of the changes in glaucoma patients results from cell metabolism disorder caused by long-term drug therapy with a preservative (BAC). Our study found a significant association between the presence of intrastromal fine inclusions and the duration of previous drug therapy in patients with POAG ($p < 0.001$).

The activation of the corneal stroma keratocyte nuclei was of a secondary nature and was more pronounced in cases when there was intense edema of the anterior stroma, i.e. in patients in the main group.

Morphological changes of the posterior corneal epithelium (endothelium) were similar between the studied groups, although there was somewhat higher percentage of these in glaucoma patients.

Many of detected corneal changes were also found in the control group, although in substantially fewer cases (Fig. 7). Thus, they cannot be ascribed as being typical signs of glaucoma process but could be explained as manifestations of DES (for example, as excessive epithelium desquamation). Some of changes may be associated with age [29]. However, the disturbance of the row order and morphology of superficial epithelial cells with the decline of their barrier function, the development of edema, including the basal epithelium, and the depletion of the superficial nervous plexus may be related to the toxic effect of preservative during a long-term use of IOP-lowering drops (Fig. 6). That is why the study of the state of cornea and conjunctiva in patients with POAG after switching to an IOP-lowering drug without preservative is of special interest.

The first preservative-free IOP-lowering drug that became available in the Russian Federation, in 2011, was Timolol-POS® (Ursapharm, Germany). POAG monotherapy patients who switched to the strike demonstrated not only an improvement in tolerability of treatment, state of the corneal epithelium, and tear film stability (according to the TBUT test), but also a decline in the need for “artificial tears”, which lowered the treatment cost [2]. However, timolol use in the population is restricted due to its systemic side effects. Furthermore, it is well known that the hypotensive effect of beta-blockers declines with time, requiring the prescription of additional IOP-lowering drops. That is why the registration of taluprost in monodoses (without preservative) in the Russian Federation in 2013 was perceived as important measure. IOP-lowering drops without preservative have been used for more than 10 years, and many experts in the world prefer to prescribe them even as first-line glaucoma treatment.

Tallotan® (Santen, Japan) was the first prostaglandin F2α analog without preservative. It combines maximum efficiency (resulting in a 35% intraocular pressure drop with once-daily dosing

![Fig. 3.](image1)  Depletion of the superficial nerve plexus (with thinning of nerve filaments and an increased coiling) in patients with primary open-angle glaucoma following treatment with medications containing benzalkonium chloride

![Fig. 4.](image2)  Moderate edema of the anterior stroma with activation and keratocyte nuclei damage, and the presence of fine hyper-reflective inclusions, in a primary open-angle glaucoma patient following long-term medical therapy; his medication included benzalkonium chloride as a preservative
regimen) and high safety profile. Its molecule exhibits a great affinity to FP-receptors, which not only provides a more pronounced IOP-lowering effect but also reduces the intensity of local adverse events such as conjunctival hyperemia and hyperpigmentation of the eyelid skin and the iris [22, 28, 33]. There have been reports on neuroprotective effects of tafluprost [34]. The drug underwent one of its essential clinical study phases in leading clinics of our country and received a favorable review [3, 4]. After registration of the drug in the Russian Fed-
Fig. 8. Dynamic pattern of the tear film stability test (the TBUT-test) in the patient group that received prostaglandin analog treatment. The initial mean values for the right (1) and left (2) eyes were 4 s, improving to 6 s a month after switching to Taflotan®; there was a tendency to its decrease after patients returned to the previous therapy (latanoprost with benzalkonium chloride).

Fig. 9. Changes in the corneal superficial epithelium in a patient with primary open-angle glaucoma after therapy with latanoprost with benzalkonium chloride: cell borders are badly visible, cells are edematous, their row order is disturbed, and nuclei show increased reflectivity.

Fig. 10. Edema and degenerative inclusions of anterior corneal stroma in a patient with primary open-angle glaucoma following the use of latanoprost with benzalkonium chloride.

Fig. 11. Improvement of the initial state (a) of the corneal superficial epithelium a month after switching to tafluprost without preservative (b), showing recovery of the epithelial cell row order, decrease in cell edema, more visible borders, and a decrease in nuclei reflectivity intensity.
TBUT-test parameters (Fig. 8, Table 2). In 47% of patients, the conjunctival hyperemia intensity (as assessed using the ORA scale) decreased after switching to Taflotan® even though its active ingredient also was a prostaglandin F2α analog \((p < 0.001)\). In addition, an improvement in corneal status was recorded after switching to the new IOP-lowering drop regimen without preservative, including recovery of superficial epithelial layer row orders (Fig. 11), and decrease in epithelium desquamation, signs of toxic injury to epithelial cells, and intensity of stromal edema \((p < 0.05)\).

Data on the improvement of the main studied parameters in glaucoma patients who received Taflotan® are presented in Table 2. In accordance to the study design, patients who switched to Taflotan® after a month returned to the previous latanoprost therapy with BAC. It was interesting that 2 weeks after the return to previous therapy, a trend emerged in the patient group of a decrease in tear film stability and deterioration of the tolerability of the drug treatment (Fig. 8).

Thus, glaucoma treatment with IOP-lowering drugs without preservative is not only effective and safe but also improves the state of the epithelium and the corneal stroma as well as the drug treatment tolerability. Instillation of a drug of this group causes less discomfort than that experienced with antiglaucoma drops that are identical in pharmacological properties but include a preservative.

To sum up, it may be stated that the use of preservative-free therapy for glaucoma patients is certainly a promising trend in modern ophthalmology. Its advantages are obvious. If it is impossible to avoid using a preservative in antiglaucoma drops, drugs with less toxic preservatives can be prescribed. In our country, Travatan® with Polyquad and Alphagan P® with Purite® have been registered.

Currently in the Russian Federation, a practicing ophthalmologist has just three preservative-free anti-glaucoma drugs at his or her disposal: TimololPOS® in the COMOD® system, Xonel® BK (betaxolol in monodoses), and a single preservative free prostaglandin F2α analog, Taflotan®. In December 2015, the combined IOP-lowering drug Tapticom® (tafluprost with timolol, without preservative) was registered, receiving favorable reports from foreign and domestic experts [32]. It will soon be available in pharmacies.

The prescription of IOP-lowering drops without preservative is especially indicated in patients with DES, with allergy, or at combined therapy, as well as in young people with a long life expectancy. The improvement of drug tolerability and quality of life of glaucoma patients will boost treatment compliance and adherence to the prescribed instillation regimen, and this would help to reduce the risk of disease progression.

**REFERENCES**


29. Нидерер RL, Перумал D, Шервин T, Мичи DN. Age-related differences in the normal human cornea: a laser scanning in vivo...
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Questions of Ophthalmic Pharmacology


