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# Impact of prostaglandin analogues on the likelihood of macular edema development in a model of autoimmune uveitis against the background of ophthalmotonus pressure

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**We conducted experimental tests to settle the debatable issue of whether the use of prostaglandin analogs in patients receiving them perioperatively during phacoemulsification might trigger macular edema. A model of steroid glaucoma was created in animals, and then, autoimmune uveitis was mimicked against the background of ophthalmotonus pressure - an inflammatory process that results in pathomorphological changes similar to those observed during phacoemulsification. Azarga and Taflotan were administered to create animal models against the above-mentioned background. These studies aimed to experimentally detect, in a comparable manner, the risk of developing macular edema in animals in the context of the administration of prostaglandin analogues, as well as to investigate the impact on the retina's vascular system. The studies found that Taflotan, when compared to Azarga, had a more noticeable negative effect on the diameter and quantity of functional capillaries in the retina against the background of the uveitis model. The administration of Azarga against the background of this model resulted in a decrease in the diameter of functional capillaries (despite an increase in their number), which exceeded the baseline values by just 2.6% (P=0.471). A reverse pattern was revealed with Taflotan administration. The functional capillaries in this group showed an increase in diameter (against the background of a decrease in their number), outperforming the intact capillaries by 15.9% (P=0.002). When used against the uveitis background, Taflotan administration raises the risk of macular edema by 26.7% (P=0.662), while Azarga decreases it by 8.3% (P=0.852). There is statistically no evidence to support the hypothesis that animals treated with Taflotan were more likely to develop macular edema than those treated with Azarga (P=0.442). Both of the tested medications do not raise the risk of getting ME in the glaucoma model. It can be concluded that Taflotan, in the absence of inciting conditions such as an inflammatory process, does not increase the likelihood of developing ME.**

***Keywords:*** *Macular edema, microcirculatory network, glaucoma, uveitis, prostaglandins, taflotan, azarga*

## INTRODUCTION

Macular edema (ME) is a disorder when the macular region of the retina of the eye (RoE) becomes edematous due to an accumulation of excess fluid. ME manifestations can range from mild ones that hardly affect vision to severe ones that cause substantial visual impairment. Numerous factors can lead to ME, such as diabetic retinopathy, age-related changes, inflammatory illnesses, glaucoma, vascular abnormalities, including vascular occlusion, reticulopathy, etc. (Iftikhar et al., 2023). Prostaglandins (PG) are inflammatory mediators that play a crucial role in many areas of eye physiology and pathology, including the development of ME. PGs, particularly PGE2, have the ability to exacerbate inflammatory processes in vascular tissue, which may enhance the permeability

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of the vascular wall and cause fluid to build up in the macular region. PGs also play a role in blood flow regulation in RoE. Impairment of this control may lead to insufficient blood flow to the macular region or insufficient pumping of fluid from capillaries into tissues (Miyake and Ibaraki, 2002). Vascular growth factors, including vascular endothelial growth factor (VEGF), which is essential for the emergence of vascular alterations and ME, can be affected by PGs in terms of their intensity (Jiang et al., 2017). According to the results of some studies, taking PG medicines such as latanoprost and bimatoprost may help prevent the development of ME. This could be due to their capacity to enhance blood flow to the eye and reduce the intensity of vascular growth factors (Holló et al., 2020). Currently, research is being conducted to develop targeted treatments, including PG receptor inhibitors, which may offer novel approaches to the treatment of ME by inhibiting PG signaling pathways. These findings highlight the complex nature of the function of PG in the pathophysiology of ME and the possibility of utilizing PG medications in its treatment (Farnoosh et al., 2021, Urias et al., 2017). However, more research is needed to completely understand their mechanisms of action, as well as to determine their efficacy and safety.

Prostaglandin analogues (PGA), such as tafluprost, etc. are now routinely utilized in ophthalmology to lower intraocular pressure (IOP). These drugs have a convenient mode of administration with a satisfactory reduction in IOP in glaucoma. Nonetheless, other authors contend that PGAa might be the root cause of ME in patients with open-angle glaucoma (OAG) after cataract extraction (Phacoemulsification or PHACO) (Fakhraie et al., 2019).

We conducted experimental tests to settle the contentious issue of whether the use of PGAs in patients receiving them perioperatively during PHACO might trigger ME. A model of steroid glaucoma (Javadova, 2023) was created in animals, and then, autoimmune uveitis was mimicked against the background of ophthalmotonus pressure - an inflammatory process that results in pathomorphological changes similar to those observed during Phacoemulsification. The model obtained this way is similar to human iatrogenic glaucoma in many aspects, such as morphology and clinical features (Javadova, 2024). Next, the study drugs were instilled into the eyes of animals.

These studies aimed to experimentally detect, in a comparable manner, the risk of developing ME in animals in the context of the administration of PGAs, as well as investigate the impact on the retina's vascular system.

## MATERIALS AND METHODS

The experiments were carried out on genus "chinchilla" rabbits, weighing 2.80-3.00 kg. In compliance with Directive 2010/63/EU of the European Parliament and of the Council of the European Union of September 22, 2010, on the protection of animals used for scientific purposes, all experimental animals were housed in conventional vivarium conditions. The animals were reused in all cases where the experimental conditions allowed doing so.

The animals were divided into 10 groups:

The 1st group (3 rabbits, 6 eyes), included the rabbits in an intact state.

An intact animal model of experimental steroid glaucoma was modeled in group 2 (8 rabbits).

In group 3 (8 rabbits), Azarga, a fixed combination medication consisting of 1% brinzolamide and 0.5% timolol maliate, was instilled into the eyes of the animals against the background of 30-day experimental glaucoma.

In group 4 (8 rabbits), Taflotan (Santen, Japan), a PGA without preservatives containing 0.0015% tafluprost solution, was instilled into the eyes of the animals against the background of 30-day experimental glaucoma.

In group 5 (8 animals), the animals were sensitized by normal horse serum (NHS) against the background of experimental glaucoma.

The animals in group 6 (8 animals) were instilled with Azarga in their eyes after the sensitization by NHS.

The animals in group 7 (8 animals) were instilled with Taflotan in their eyes after the sensitization by NHS.

In group 8 (8 animals), the animals were sensitized by normal horse serum (NHS) against the background of experimental glaucoma. Then they received a shocking dose of NLS

intravitreally, resulting in uveitis.

The animals in group 10 (8 animals) were instilled with Azarga in their eyes against the background of uveitis.

The animals in group 10 (8 animals) were instilled with Taflotan in their eyes against the background of uveitis.

The experimental glaucoma model was created by administering one drop of 1% dexamethasone solution to each of the rabbits' eyes for 30 days. The long modeling time was chosen taking into account the fact, that persistent, irreversible glaucoma-related changes start to take place with prolonged use of steroids. This approach was chosen since it served the study's purposes, as the rabbits not only developed glaucoma but also cataracts. The model obtained this way is similar to human iatrogenic glaucoma in many aspects, such as morphology and clinical features (Javadova, 2023).

The uveitis model was developed as follows (Aksenova et al., 2017): to sensitize the animals, they were first subcutaneously injected with 5 ml of NHS. This was followed by a further intramuscular injection of 1 ml of NHS after 5 days. 9 days after the last injection, a shocking 0.07 ml dose of NHS was administered intravitreally into the right eye. The left eye was used as a control. The clinical presentation of uveitis started 3 days after the administration of the shocking dose in the right eye. Then the tested preparation was instilled into both eyes of the animals.

The animals underwent intravitreal visual inspection of their eyes, ophthalmological examination of the fundus and RoE, and measurement of intraocular pressure (IOP). All procedures were carried out with a manual ophthalmoscope. Blood for immunological testing and determination of the leukocytes, neutrophils, and lymphocyte count was drawn from the ear vein. Following the completion of the experiment, the eyeballs of the animals were enucleated under anesthesia (intravenous injection of 0.5-0.6 ml of ketamine), and micropreparations were prepared for morphological studies of RoE, for reviewing the state of the vascular bed, and the presence of ME. The IOP levels were measured with a portable Tono-Pen X pneumotonometer (Reichert, USA).

An ophthalmological examination of the anterior sector of the eye, fundus, and RoE was carried out using a Welch Allyn portable ophthalmoscope (USA, Dealmed). This equipment allows for analyzing the cornea, RoE, choroid (uvea), the state of the optic disc and optic nerve, optic disc exquamation, and ME.

The circulating immune complexes **(**CIC), immunoglobulins (Ig), and lymphocytes in the blood were evaluated using an enzymatic colorimetric approach on an FP-9019 analyzer (made in Finland), while the complement components were determined based on hemolytic activity. The leukocyte, lymphocyte, and neutrophil counts were determined on an Auto Hematology Analyzer Ratyo RT-7600 (China, 2019).

Morphometry of histological sections of RoE with a thickness of 4 microns was performed under a SCOP brand microscope (Holland), which gives an increase of X 400 and the possibility of automatic photographing of enlarged section images, following the method developed by G.G.Avtandilov (Avtandilov, 2002). This was accomplished using an ocular mesh installed on the microscope and a screw ocular micrometer. The following parameters were determined based on the obtained morphometry data:

1. The number of functional capillaries per 1 $mm^2$ area (pcs)
2. The diameter of functional capillaries per 1 $mm^2$ area (microns)
3. The total area of the microcirculatory network (sq. microns)
4. The total area of the medium-diameter arteries (sq. microns)
5. The lumen of the medium-diameter arteries (microns)

The acquired digital data were statistically analyzed using IBM Statistics SPSS-22 and MS EXCEL-2016 statistical tools for variational (U-Mann-Whitney) nonparametric analysis.

## RESULTS AND DISCUSSION

Since the start of the rabbits' experimental glaucoma modeling, daily measurements of their intraocular pressure (IOP) have revealed a dynamic increase in IOP. This increase began on the third day following the initiation of dexamethasone instillation and reached 20.4 mm

Hg (maximum value of 21 mm Hg and minimum value of 19 mm Hg) from the initial 19.6 mm Hg intact value (IV) (maximum value of 20 mm Hg and minimum value of 19 mm Hg). On day thirty of the trial, a sustained rise in IOP of 54.1% (P=0.008) was noted, confirming the onset of experimental glaucoma.

On the 30th day, the instillation of Azarga and Taflotan as hypotensive agents resulted in a 37.4% decrease (P=0.002) and a 38.74% (P=0.02) decrease in IOP in the Azarga and Taflotan groups, accordingly, reaching the reference values in both groups.

A model of uveitis was created in the setting of ophthalmotonus pressure. The next day, after administering a shocking dose of NHS to the right eyes of animals, visual indicators of uveitis (clinical presentation) started to appear, which then worsened and reached a significant severity on the 3rd day. The examination of the cornea during this period revealed that all animals had 100% opacity, 100% corneal edema, 50% of cases had precipitates, 62.5% of cases had opacity on the anterior chamber, 25% of cases had hypopion, 43.75% of the total number of examined eyes had sporadic synechiae on the pupil, 12.5% of the total number of examined eyes had multiple synechiae; pupil occlusion was seen only in one eye and accounted for 6.25% of the total number of examined eyes. Also, vasodilation was observed in the iris in 3 eyes, which accounted for 18.75%, along with iris edema in 18.75%, and vitritis in 62.5% of the eyes.

Thus, the clinical presentation confirmed the development of uveitis in all animals.

Laboratory examinations of animal blood revealed (Table 1) that leukocyte content increased by 95.9% (P<0.001) and neutrophil content decreased by 22% (P=0.417) in animals against the background of sensitization by NHS without a shocking dose in the right eye (sample 2) compared with the indicators of animals with ophthalmotonus pressure before sensitization (sample 1). Following the injection of a stunning dose of NHS in the right eye (sample 3), markers of the animals changed in the following ways against the backdrop of NHS sensitization on day 3: The leukocyte count increased by 90.8% (P<0.001), and neutrophils by 105.8% (P<0.001).

The total hemolytic ability of the complement was determined, which was decreased by 84.4% (P<0.001) in the second sample and remained nearly at the same level (84.3%, P<0.001) in the third sample. The CIC content decreased by 99.1% (P<0.001) and 96.9% (P<0.001), respectively. At the same time, there was an increase of 120.5% (P<0.001) in T-lymphocyte content and 116.8% (P<0.001) in B-lymphocyte content in the second and third samples, respectively. The IgE blood levels increased more actively. IgE content in the 2nd sample increased 5.3 times (P<0.001), and in the 3rd sample, 6.5 times (P<0.001).

As the obtained results show, NHS, as an antigen, causes the generation of antibodies when injected subcutaneously. With repeated administration intramuscularly, an antigen-antibody response occurs, resulting in the formation of immune complexes with tissue affinity. The body is being sensitized. Blood levels of immune indicators increase. Administration of a shocking intravitreal dose leads to the development of an inflammatory process in the uveitis (Hsuan et al., 2021). As this takes place, the indicators of immune activation remain at a high level.

**Table 1.** Changes in immune parameters of the animal blood samples against the background of experimental glaucoma, sensitization by normal horse serum, and experimental uveitis

| Index | | Sample 1 | Sample 2 | Sample 3 |
|---|---|---|---|---|
| | **Valid N** | **16** | **16** | **16** |
| **Leukocy-tes$10^9$/L** | Mean ± Standard Error of Mean | 7.07±0.04 | 13.85±0.47 | 13.49±0.19 |
| | Minimum; Maximum | 6.90; 7.50 | 10.20; 17.10 | 12.20; 14.80 |
| | Median | 7.00 | 14.20 | 13.70 |
| | Percentile 25; Percentile 75 | 6.95; 7.15 | 12.65; 15.10 | 12.85; 14.05 |
| | $P_1$ | | 0.000 | 0.000 |
| | $P_2$ | | | 0.291 |

*Continued Table 1*

| | | | | |
|---|---|---|---|---|
| **Neutro-phils $10^9$/L** | Mean ± Standard Error of Mean | 17.3±0.4 | 16.7± 0.5 | 35.6±0.4 |
| | Minimum; Maximum | 14.5; 20.1 | 12.1; 21.3 | 33.2; 38.1 |
| | Median | 17.1 | 16.7 | 35.6 |
| | Percentile 25; Percentile 75 | 16.3; 18.6 | 15.8; 17.6 | 34.9; 36.5 |
| | $P_1$ | | 0.417 | 0.000 |
| | $P_2$ | | | 0.000 |
| **Compli-мент с.u.** | Mean ± Standard Error of Mean | 7.07±0.04 | 1.10±0.02 | 1.11±0.02 |
| | Minimum; Maximum | 6.90; 7.50 | 1.00; 1.20 | 1.00; 1.20 |
| | Median | 7.00 | 1.10 | 1.10 |
| | Percentile 25; Percentile 75 | 6.95; 7.15 | 1.00; 1.20 | 1.00; 1.20 |
| | $P_1$ | | 0.000 | 0.000 |
| | $P_2$ | | | 0.841 |
| **CIC с.u.** | Mean ± Standard Error of Mean | 17.28±0.39 | 0.16±0.00 | 0.54±0.02 |
| | Minimum; Maximum | 14.50; 20.10 | 0.15; 0.18 | 0.40; 0.60 |
| | Median | 17.10 | 0.16 | 0.55 |
| | Percentile 25; Percentile 75 | 16.30; 18.60 | 0.15; 0.17 | 0.50; 0.60 |
| | $P_1$ | | 0.000 | 0.000 |
| | $P_2$ | | | 0.000 |
| **T- Lympho-cytes $10^9$/L** | Mean ± Standard Error of Mean | 2.20±0.15 | 4.85±0.16 | 4.77±0.15 |
| | Minimum; Maximum | 1.20; 3.00 | 3.90; 5.90 | 3.90; 5.90 |
| | Median | 2.15 | 4.85 | 4.70 |
| | Percentile 25; Percentile 75 | 1.75; 2.80 | 4.40; 5.15 | 4.40; 5.05 |
| | $P_1$ | | 0.000 | 0.000 |
| | $P_2$ | | | 0.650 |
| **B – Lympho-cytes $10^9$/L** | Mean ± Standard Error of Mean | 2.86±0.23 | 5.52±0.29 | 5.52±0.29 |
| | Minimum; Maximum | 1.40; 4.30 | 3.80; 7.30 | 3.80; 7.30 |
| | Median | 2.85 | 5.40 | 5.40 |
| | Percentile 25; Percentile 75 | 1.95; 3.80 | 4.50; 6.50 | 4.50; 6.50 |
| | $P_1$ | | 0.000 | 0.000 |
| | $P_2$ | | | 1.000 |
| **IgE кЕдА/л** | Mean ± Standard Error of Mean | 0.23±0.02 | 1.21±0.09 | 1.49±0.14 |
| | Minimum; Maximum | 0.00; 0.35 | 0.50; 2.17 | 0.56; 2.89 |
| | Median | 0.22 | 1.19 | 1.28 |
| | Percentile 25; Percentile 75 | 0.19; 0.29 | 1.00; 1.30 | 1.20; 1.74 |
| | $P_1$ | | 0.000 | 0.000 |
| | $P_2$ | | | 0.065 |

*Sample 1 - against the background of experimental glaucoma, Sample 2 – against the background of sensitization by normal horse serum, and Sample 3 – against the background of experimental uveitis.*

*$P_1$ – the statistical significance of the differences as compared to Sample 1*

*$P_2$ – the statistical significance of the differences as compared to Sample 2*

*Wilcoxon Mann-Whitney Test*

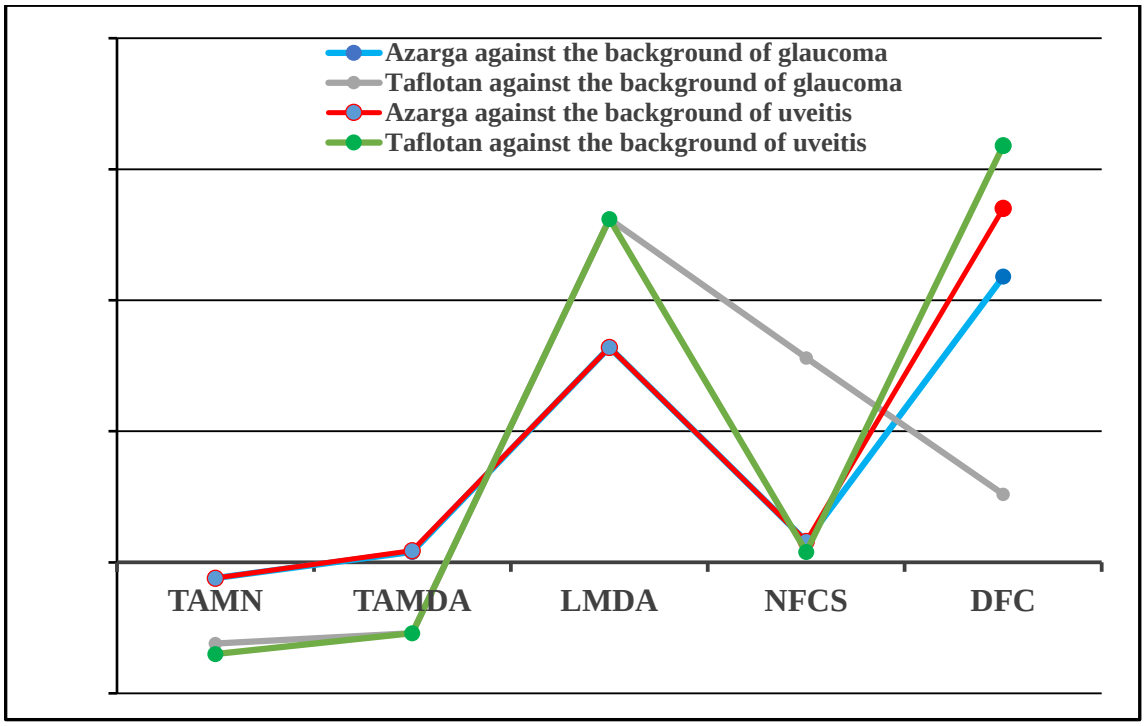


**Fig. 1.** Changes in the vascular bed of the retina of the eye caused by hypotensive agents (Azarga and Taflotan) against the background of an experimental glaucoma model and autoimmune uveitis in the setting of ophthalmotonus pressure.

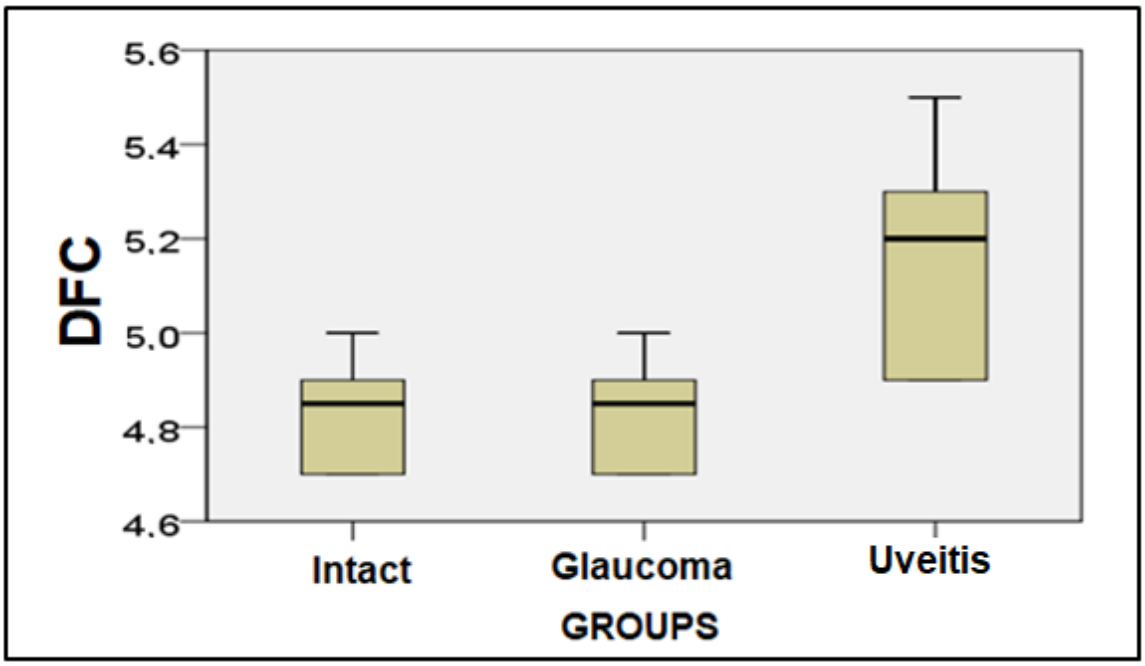


**Fig. 2.** Changes in the diameters of the functional capillaries of the retina of the eye with instillation of Azarga and Taflotan against the background of an experimental glaucoma model, and autoimmune uveitis in the setting of ophthalmotonus pressure.

The study of the changes in the vascular bed of RoE (Fig. 1) in the course of modeling autoimmune uveitis against the background of ophthalmotonus pressure showed that the total area of the microcirculatory network (TAMN) of RoE of the animals in which experimental glaucoma was modeled was reduced by 2.2% compared with IV (P=0.178). TAMN began to recover in animals treated with Azarga and Taflotan as a hypotensive drug against the background of the glaucoma model, and it remained at a level 0.6% less than IV throughout the trial period (P=0.641). In animals with the experimental autoimmune uveitis model against the background of ophthalmotonus pressure, this parameter is slightly higher than IV (by 0.3%, P=0.934). With the injection of the antihypertensive drugs into the eyes of animals against the backdrop of the uveitis model, the TAMN dropped by 3.1% (P=0.169) and by 3.5% (P=0.102) against the background of Azarga and Taflotan administration, respectively.

The total area of medium-diameter arteries (TAMDA) of RoE against the background of the glaucoma model, was slightly higher than IV (by 1.4% at P=0.681). TAMDA was decreasing in the animals receiving Azarga and Taflotan in their respective groups against the background of the glaucoma model, and it remained at a level 0.6% less than IV throughout the trial period (P=0.641). In the animals in which experimental autoimmune uveitis occurred against the background of ophthalmotonus pressure, TAMDA increased by 0.3% (P=0.806). The TAMDA dropped by 2.7% (P=0.292) in the animals whose eyes were instilled with Azarga against the backdrop of the uveitis model. Similar changes were taking place against the background of the Taflotan administration. In this group, TAMDA also decreased by 2.7% (P=0.292).

The lumen of the medium-diameter arteries (LMDA) increased by 6.5% (P=0.142) against the background of the glaucoma model. With the instillation of Azarga in the eyes of the animals with ophthalmotonus pressure against the background of the glaucoma model, the LMDA increased even more and exceeded the intact values by 8.5% (P=0.076), while in the animals treated with Taflotan under equal conditions, it increased by 8.2% (P=0.076). As it can be seen, the difference between the groups is negligible and statistically insignificant. As the presented data show, both studied drugs exert practically the same impact on LMDA against the steroid glaucoma model, resulting in a slight and statistically insignificant expansion of their lumen. However, changes were observed in all animals in both groups. Changes in the LMDA in the retina of the eyes of the animals upon modeling of autoimmune uveitis against the background of ophthalmotonus pressure were not detected. This indicator was also increased by 8.2% as compared to IV (P=0.120). Administration of the studied preparations in both groups led to even more increases in LMDA (by 13.1%, P=0.027).

The number of functional capillaries (NFCs) per 1 $mm^2$ (Fig. 2) of the RoE near the macular region against the background of an experimental glaucoma model diminished slightly (by 1.6%, P=0.809). The instillation of the studied antihypertensive agents in both groups led to a slight increase in NFC, where NFC exceeded IV by 0.8% (P=0.555). After modeling the autoimmune uveitis, NFC increased by 2.4% (P=0.411) (as compared to IV). In this case, the administration of Azarga increased NFC by 7.8% (P=0.097), and Taflotan increased NFC by 0.4% (P=0.052).

The diameter of functional capillaries (DFC) per 1 $mm^2$ area remained unchanged against the background of the experimental steroid glaucoma model. However, the administration of Azarga resulted in an increase in DFC in all animals by an average of 10.9% (P=0.026), and with Taflotan, this increase was 13.5% (P=0.004). Compared with IV, this indicator increased by 12.9% (P=0.022) against the background of the uveitis model. The administration of Azarga against the background of this model resulted in a decrease in DFC (in the setting of an increase in their number), which exceeded the IV by just 2.6% (P=0.471). A reverse pattern was revealed with the Taflotan administration. DFC in this group showed an increase (against the background of a decrease in their number), exceeding the intact capillaries by 15.9% (P=0.002).

The results of the macula examination in the eyes of rabbits for the presence of ME are shown in Table 2. The data presented in the table show that none of the six intact rabbits have experienced changes in the macula, and ME is

absent in 100% of observations.

**Table 2.** Macular edema in the eyes of rabbits detected during the examination of the fundus with a manual ophthalmoscope

| | | Groups | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | **Intact** | **Glaucoma model** | **Glaucoma - sensitized** | **Uveitis** | **Sensitization – Azarga** | **Sensitization – Taflotan** | **Uveitis - Azarga** | **Uveitis - Taflotan** |
| **ME is absent** | Count | 6 | 5 | 5 | 1 | 6 | 2 | 2 | 0 |
| | Column N % | 100.0% | 83.3% | 83.3% | 16.7% | 75.0% | 25.0% | 25.0% | 0.0% |
| **ME present** | Count | 0 | 1 | 1 | 5 | 2 | 6 | 6 | 8 |
| | Column N % | 0.0% | 16.7% | 16.7% | 83.3% | 25.0% | 75.0% | 75.0% | 100.0% |

In the eyes of animals, with the glaucoma model, ME was detected in one rabbit out of six examined, amounting to 16.7% (P=0.699) (according to the Mann-Whitney test results). The situation with the sensitized is similar, with ME detected only in one rabbit. Examination of the fundus of six animals with the uveitis model revealed the development of ME in five of them, amounting to 83.3% (P=0.015). In sensitized animals, ME was observed against the background of Azarga administration in two rabbits out of eight, which was 25% of all animals (P=0.491), whereas in animals treated with Taflotan, ME was detected in six animals, which was 75% (P=0.020). In the uveitis model rabbits, ME was detected in six animals (75%, P=0.020) against the background of Azarga administration, and ME was detected in all animals (100%, P=0.001) treated with Taflotan.

As it seems from the results, with the use of Taflotan against the background of sensitization and the uveitis model, as well as with the administration of Azarga against the background of uveitis, the development of ME is statistically confidently established in settings of uveitis.

Our research has demonstrated that not only the inflammatory process in the eyes (with uveitis) but also overall body sensitivity increases the probability of the development of ME. The administration of an AHP (Taflotan) in the animals sensitized by the NHS increases the likelihood of ME development.

Thus, the likelihood of developing ME against the background of experimental autoimmune uveitis is very high in all groups, and the sensitization of the organism by NHS also increases the likelihood of developing ME against the background of an AHP administration. That being said, the sensitization of rabbits by NHS against the background of an experimental glaucoma model does not affect the likelihood of ME development, with this likelihood not being statistically confirmed (P=1.000). However, hypotensive agents may provoke the development of ME in sensitized animals. Thus, with the instillation of Taflotan, a prostaglandin derivative, the likelihood of the development of ME is 58.3% higher as compared to sensitized animals, while with Azarga, this difference is 8.3% (P=0.852). It is evident that sensitized animals instilled with Taflotan have a 50% higher chance of developing ME than the animals injected with Azarga, but this likelihood is not supported by statistical evidence (P=0.105).

As previously demonstrated, when a shocking dose of NHS is administered into an animal's eye that has become sensitized, this is resolved by uveitis development, leading to an increase in the likelihood of developing ME up to 62.6% as compared to the unsensitized animals. However, such a difference, as defined by a percentage, is statistically insignificant. When used against the uveitis background, Taflotan administration raises the risk of ME by 26.7% (P=0.662), while Azarga decreases it by 8.3% (P=0.852). There is statistically no evidence to support the hypothesis that animals treated with Taflotan were more likely to develop ME than those treated with Azarga (P=0.442). Changes in the RoE microcirculation promote the effusion of fluid from the blood vessels, and because the RoE macular region is prone to ME because of its anatomical makeup, ME is mostly seen there (Mack et al., 2022, Yuan et al., 2024). Our study's findings support this once more.

Thus: 1. With the administration of dexamethasone to model glaucoma in rabbits, the animals developed a persistent ophthalmotonus pressure that did not dissolve after the termination of the administration of the preparation.

2. Hypotensive agents such as Azarga and Taflotan reduced IOP almost equally.

3. Instillation of Azarga and Taflotan against the background of an autoimmune uveitis model created by NHS in animals with ophthalmotonus pressure showed that these agents have an effect on the vascular bed of the retina of the eye, while statistically significant changes are observed with the administration of Taflotan. These changes consist mainly of the increase in DFC

4. Compared to Azarga, the administration of Taflotan in sensitized animals, and animals with experimental uveitis under ophthalmotonus pressure also resulted in considerably higher incidences of ME among the animals. However, despite the substantial percentage value of these indications, the data lack statistical reliability, making it impossible to state categorically that prostaglandin analogues may be the causes of ME in similar cases. It should also be noted that in the glaucoma model, neither Taflotan nor Azarga led to the development of ME in the animals.

## CONCLUSION

According to the result of an experimental study, in response to the debatable question of the possibility of long-term AHP administration causing ME, it may be concluded that Taflotan, in the absence of provoking factors, for example, an inflammatory process, does not result in an increase in the likelihood of developing ME. Overall sensitization of the body also increases the likelihood of ME development. Therefore, in order to avoid an increased risk of developing ME during PHACO in patients with OAG combined with cataracts, it is recommended that for perioperative prescription of AHPs, along with other routine examinations, a blood count should be done to identify the patient's immune status.

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