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Therapeutic options in the treatment of open angle glaucoma and their use in accordance with the latest guidelines

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HIGHLIGHTS

The goal of pharmacological treatment of glaucoma is to achieve the target pressure with a single drug, a combination of drugs or a combined drug.

ABSTRACT

Glaucoma is an optic neuropathy characterized by typical damage of the optic nerve with gradual atrophy of retinal ganglion cells and visual field defects. The goal of glaucoma therapy is to reduce intraocular pressure and reduce daily pressure fluctuations. Currently, in the treatment of primary open-angle glaucoma in Poland, we use four groups of drugs: β-adrenergic receptor antagonists, prostaglandin analogues, α-adrenergic receptor agonists and carbonic anhydrase inhibitors. First-line drugs, according to the guidelines of the Polish Ophthalmological Society, are prostaglandin analogues/prostamide. When considering the addition of a second drug to prostaglandins, brimonidine lowers intraocular pressure more strongly than dorzolamide or brinzolamide, similarly as timolol does. Drug containing two active substances are as effective as substances administered in two separate drops, therefore it is advantageous to use combined drug instead of using two different drugs.

Key words: glaucoma, pharmacological therapy, glaucoma drugs, combined drugs

INTRODUCTION

Glaucoma is a neuropathy of the optic nerve that affects approximately 2% of the population, mostly those over the age of 50. It is characterized by damage to the optic nerve, gradual atrophy of retinal ganglion cells, and specific visual field defects. Elevated intraocular pressure (IOP) is one of the most significant risk factors for glaucoma. Numerous risk factors for glaucoma have been described and proven. The objective of pharmacotherapy for glaucoma, aimed at protecting the optic nerve, is to reduce IOP and minimize diurnal fluctuations. However, it is important to note that not all patients will experience a reduction in IOP sufficient to halt the progression of glaucoma.

Treatment of primary open angle glaucoma (POAG) may include:

1. Pharmacological treatment:
   - topical eye drops containing IOP-lowering drugs
   - in cases where one type of treatment is insufficient, it may be necessary to use a combination of different drugs.
2. Laser treatment:
   - laser trabeculoplasty – improves outflow of aqueous humor from the eye, and thus helps reduce IOP.
3. Surgical treatment:
   - trabeculectomy
   - drainage implants
   - microinvasive glaucoma surgery.
4. Lifestyle changes:
   - avoiding factors that can increase IOP
   - a healthy diet and moderate regular physical activity.

DRUG CLASSES USED IN THE PHARMACOTHERAPY OF PRIMARY OPEN ANGLE GLAUCOMA

There are currently several glaucoma preparations available on the market, each containing various active substances. In Poland, four main groups of drugs are used to treat POAG:

- β-adrenergic blockers
- prostaglandin analogs
- α-adrenergic receptor agonists
- carbonic anhydrase inhibitors (RHO kinase inhibitors are a new group of drugs available worldwide, but not yet in Poland).

Some preparations may contain a single or a combination of two active ingredients. Excluding pilocarpine, which is no longer used in POAG treatment, the drugs used for the longest period of time are timolol (since 1978), dorzolamide (since 1994), latanoprost with brimonidine (since 1996), and brinzolamide (since 2000). Other active substances have only been introduced in the 21st century [1].

Beta-adrenergic receptor antagonists (β-blockers) inhibit the effects of catecholamines by affecting β-adrenergic receptors. Beta-blockers lower IOP by inhibiting the secretion of aqueous humor from the ciliary body epithelium through the inhibition of cyclic AMP production.

Five β-blockers are used globally to treat glaucoma: betaxolol, carteolol, levobunolol, metipranolol, and timolol. The primary representative of this group is timolol, a non-selective antagonist of β-adrenergic receptors, blocking both type 1 and type 2 β-receptors. Betaxolol is a cardioselective β-blocker, exerting a stronger effect on type 1 β receptors and causing less bronchospasm. Carteolol results in a lesser decrease in blood pressure during nighttime hours. Levobunolol and metipranolol are not available in Poland. The use of this combination drug decreases IOP within the first hour of administration, and this effect can last for up to four weeks after discontinuation of use.

However, due to the predominance of the parasympathetic nervous system during sleep, the effect of these drugs diminishes at night. Additionally, once the drug enters the bloodstream, it can cause systemic side effects and lower IOP in the other eye. If the patient is also using β-blockers to treat general diseases, the effectiveness of the topical treatment may be significantly lower than the standard 20–30% [2, 3].

It should be noted that the use of this group of drugs is not recommended for individuals with bronchial asthma, obstructive lung disease, congestive heart failure, atrioventricular conduction disorders, or bradycardia. Beta-blockers may cause rare side effects, including those related to the respiratory and cardiovascular systems, lipid disorders, endocrine disorders (such as exacerbation of hyperthyroidism), and neurological and psychiatric symptoms. Some side effects occur immediately at the beginning of therapy, while others may only manifest after prolonged substance use [2, 4].

Prostaglandin analogs are the second most important group of drugs used to lower IOP. They stimulate prostaglandin receptors in the ciliary body, which increases aqueous humor outflow through the unconventional choroidal-arterial pathway. Connective tissue remodeling and widening of the intermaxillary spaces in the ciliary body result in a reduction of IOP by approx. 30%. It should be noted that the maximum drop in pressure is observed even after nearly 10 h after infusion. However, it is important to keep in mind that some patients may not respond to prostaglandin analogs, which may require a change in medication [1, 2].

Prostaglandins act on pro-inflammatory prostaglandin (E-type) receptors, which can exacerbate inflammation in conditions such as inflammatory glaucoma or neovascular glaucoma. Prostaglandin analogs come in the form of esters or amides (prostamides), and only the acid form of the drug is active. They are typically used once daily in the evening to maintain effectiveness. Latanoprost, travoprost, tafluprost, and bimatoprost are all effective in reducing IOP. Bimatoprost is the most effective, reducing IOP by 27–33%, while latanoprost and travoprost reduce IOP by about 25–32%

and tafluprost by 27–31% [3]. A meta-analysis conducted by Stewart et al. also found that bimatoprost was the most effective in reducing IOP, even more so than the combination drug dorzolamide and timolol, which reduced IOP by 26% [5].

The mechanism of action of α-adrenergic receptor agonists is to stimulate alpha-2 (α_2) adrenergic receptors that mediate vasoconstriction, decrease aqueous humor production, and increase choroidal outflow. Although their neuroprotective effects are possible, there is insufficient scientific evidence to confirm this [2, 4]. In Poland, only brimonidine eye drops are currently used in Poland to treat glaucoma. This substance reduces IOP by nearly 20–30%, with maximum effect achieved 2 h after infusion [3].

When using brimonidine, it is important to avoid administering it to young children and patients taking tricyclic antidepressants or MAO inhibitors. It is also important to monitor the patient's blood pressure due to brimonidine's strong hypotensive effect. Additionally, fatigue, lethargy, or dry mouth may occur during use. It is important to note that brimonidine does not lower IOP at night [3].

Carbonic anhydrase inhibitors block carbonic anhydrase II, which is involved in the production of aqueous humor by the ciliary processes. Inhibition of this enzyme leads to a decrease in the secretion of aqueous fluid, resulting in a 15–20% reduction in IOP [3]. It is important to note that these pharmaceuticals belong to the sulfonamide derivative class. Therefore, people who have been diagnosed with hypersensitivity to sulfonamides should not use them. There are two topical drugs, dorzolamide and brinzolamide, available for use, as well as an oral formulation, acetazolamide. It is worth noting that an intravenous drug is also available in other countries [2].

PHARMACOTHERAPY WITH A SINGLE DRUG

The objective of anti-glaucoma therapy is to reduce IOP to target levels, which are specific to each patient and correspond to the IOP at which disease progression is minimized. This approach aims to maximize the patient's quality of life over time. There is no single safe IOP level for all patients. However, in early glaucoma, it is recommended to plan for an IOP reduction of at least 20%, and in more advanced stages, the reduction should be even greater. If progression is observed despite reaching the target pressure, a new, lower IOP should be set as the target pressure [4]. Thus, the patient's target IOP should be adjusted during follow-up visits and modified as needed. The Early Manifest Glaucoma Trial (EMGT) demonstrated that reducing IOP by 1 mmHg can decrease the progression of glaucomatous lesions by up to 10% [6].

According to the Polish Society of Ophthalmology (PTO) guidelines, treatment should be initiated only after conducting all necessary tests, provided that the initial IOP is not high and the glaucomatous damage is not severe. Before starting treatment, it is crucial to measure the patient's IOP at least once using the best available method, preferably applanation. Monotherapy is the recommended approach at the beginning of treatment, and therapy for each eye should be planned separately. When selecting a medication, it is important to consider the patient's well-being, including overall safety, minimizing local adverse reactions, patient compliance and quality of life, cost of the drug, and the effectiveness of the drug in lowering IOP [1]. According to the PTO, the first-line drugs are prostaglandin analogs and prostamides. These should be prescribed after a thorough patient history, including general illnesses and medications [4]. If the patient has an abnormal tear film or other abnormalities in the ocular surface, preservative-free medications should be considered.

If the target IOP is not achieved, we should consider changing the medication or adding a second drug. After initiating treatment, it is important to monitor the patient's IOP. It is crucial to monitor not only the IOP but also the patient's tolerance of the drug and potential adverse reactions.

Prostaglandins are the most potent topical therapies available for lowering IOP. They are administered once daily in the evening and they rarely cause general side effects. Latanoprost, bimatoprost, travoprost, and tafluprost are currently available on the market. In some studies, prostamide (bimatoprost) has been demonstrated to lower IOP more effectively than other prostaglandin analogs, while in other studies, all three clinically used prostaglandin analogs were found to be equally effective.

When considering adding a second drug to prostaglandins, it is important to note that brimonidine has a more potent effect on lowering IOP than dorzolamide or brinzolamide [7].

COMBINATION DRUGS

They contain a combination of different active ingredients, often from different drug classes, that act synergistically. Combination drugs are used in glaucoma therapy to increase treatment effectiveness and improve patient adherence to medication. It is recommended to consider combination drugs in the following situations:

1. Ineffectiveness of a single drug – if treatment with a single drug does not bring the expected results in controlling IOP, a combination of substances with different mechanisms of action can be used.
2. Simplifying the treatment regimen – combination drugs simplify treatment regimens by allowing patients to use multiple active substances in a single dose, potentially increasing treatment effectiveness and improving patient compliance.

3. Minimizing side effects – the components of combination drugs are selected to minimize side effects while achieving maximum efficacy. The use of combination drugs results in a lower rate of side effects, reducing irritation of the ocular surface.
4. Reduce the risk of drug interactions – using a single formulation instead of two different drugs can reduce the risk of drug interactions. This is because both ingredients are contained in one formulation.

The following combination drugs are currently available in Poland:

- prostaglandin analog + β-blocker
- α-receptor agonist + β-blocker
- carbonic anhydrase inhibitor + β-blocker
- carbonic anhydrase inhibitor + α-receptor agonist.

Combination therapy is generally more effective than monotherapy. Formulations that contain two active substances in one package are as effective as substances administered in two separate preparations. Therefore, it is advantageous to use one compound drug instead of two separate drugs.
The combination of a prostaglandin analog and a β-blocker in a single preparation has been shown to improve patient adherence to treatment and promote a healthier ocular surface compared to separate preparations. In Poland, there are combinations of prostaglandin and prostamide analogs available with timolol.
Large-group studies have shown that a combination of latanoprost and timolol is more effective in reducing IOP than administering latanoprost once a day and timolol twice a day [8, 9]. In a recently published study, both groups had similar mean IOP after 1 and 3 months. However, after 6 months, the group treated with two separate preparations achieved better results with a mean IOP of 15.0 mmHg compared to 16.7 mmHg in the other group [10]. The prevalence of the combination drug has also been described for travoprost and timolol [11]. The combination formulation of bimatoprost and timolol lowered IOP by 0.8 mmHg compared to therapy with two separate formulations, but treatment with the combination formulation resulted in significantly less frequent anterior segment irritation and a lower percentage of patients discontinuing therapy [12]. Taflotan combined with timolol was more effective in reducing IOP than timolol alone and caused fewer side effects, such as eye irritation [13].
The combination drug containing timolol and brimonidine may offer several advantages for treating glaucoma. Timolol is a β-blocker that reduces the production of aqueous humor, while brimonidine is a sympathomimetic that increases the outflow of aqueous humor from the eye. When administered together, they have complementary mechanisms of action. The combination of these two substances can have a synergistic effect, resulting in more effective IOP reduction than using a single drug.
The combination of brimonidine with timolol administered twice daily (one drop into each eye) was found to be more effective than monotherapy (brimonidine administered twice daily and timolol 3 times daily) over periods of 3 and 12 months [14]. Additionally, the efficacy of administering brimonidine and timolol twice daily was comparable to or superior than that of the combination preparation dorzolamide with timolol used twice daily [15, 16]. Both combination drugs were safe and well tolerated. Moreover, brimonidine with timolol also scored higher on the ocular comfort test than dorzolamide with timolol. In patients receiving combination monotherapy, the reduction in IOP from baseline was 7.7 mmHg (32.3%) for brimonidine with timolol and 6.7 mmHg (26.1%) for dorzolamide with timolol. Patients taking brimonidine with timolol reported experiencing less burning, stinging, and unusual taste compared to those taking dorzolamide with timolol [17]. Previous studies have reported a comparable reduction in IOP when using these two combination drugs [18, 19].
Research has shown that using a combination of dorzolamide and timolol is more effective in lowering IOP than one medication [20]. However, when compared to combination therapy with two separate drugs, there was no significant difference in IOP reduction [21]. Combination of brinzolamide and timolol, as well as dorzolamide and brinzolamide, have been shown to reduce IOP more effectively than monotherapy [22, 23].

CONCLUSIONS

The study presents therapeutic options for treating primary open-angle glaucoma, considering the available preparations in Poland. The text describes the mechanism of action, contraindications, and possible side effects of the four main groups of drugs used to treat glaucoma. It presents the principles of pharmacotherapy with a single drug, the benefits of using a combination preparation, and the indications for it according to the guidelines of the PTO and the European Glaucoma Society, as well as the results of scientific studies.

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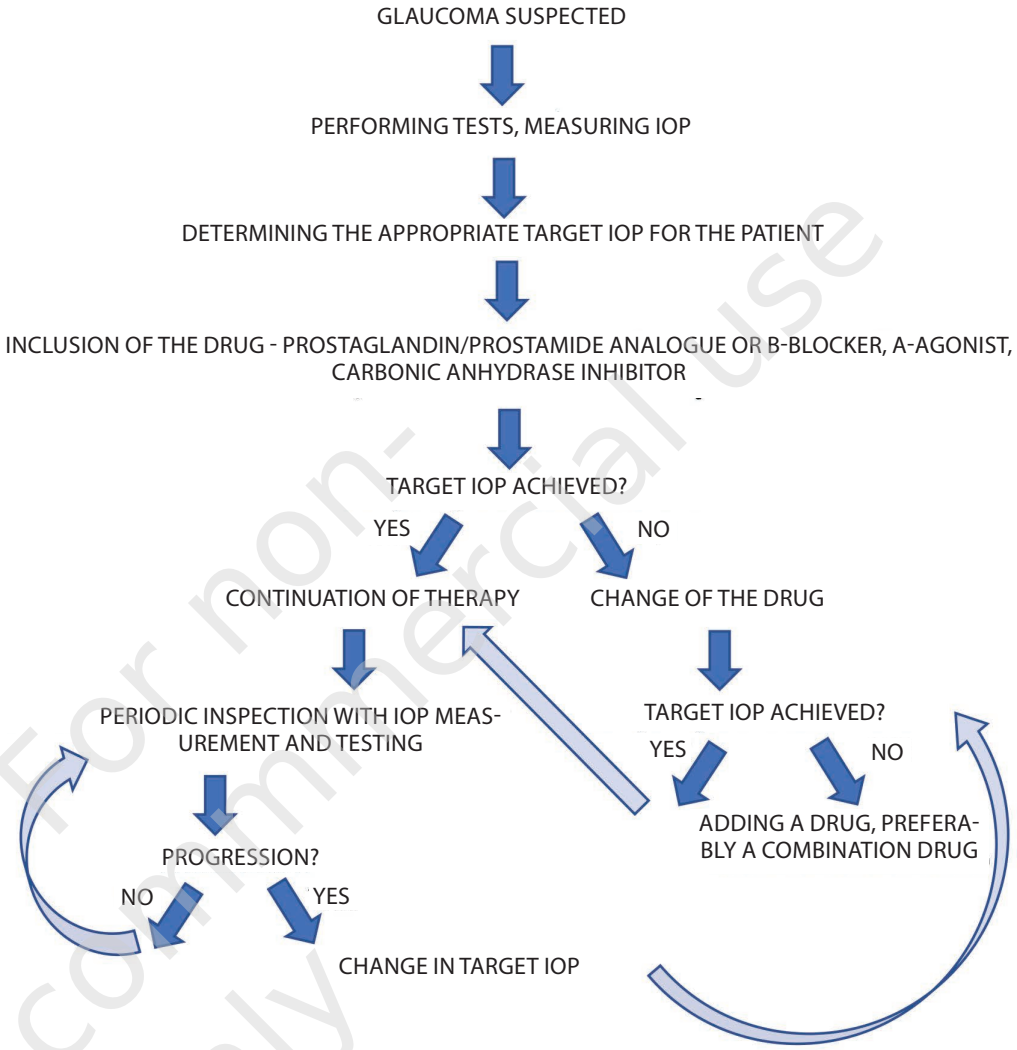
Management scheme for the inclusion of pharmacological treatment of primary open angle glaucoma.



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Marta Misiuk-Hojło: idea and design of the study, literature review, analysis and interpretation of literature data, critical evaluation of the manuscript, approval of the final version of the manuscript.
Martyna Tomczyk-Socha: literature review, analysis and interpretation of literature data, writing the manuscript, approval of the final version.

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