

CARBONIC ANHYDRASE INHIBITORS FOR THE TREATMENT OF GLAUCOMA

Strakhov VV¹, Korsakov MK² ✉, Fedorov VN^{1,2}, Vdovichenko VP³, Shetnev AA², Popova AA², Volkhin NN^{1,2}

¹ Yaroslavl State Medical University, Yaroslavl, Russia

² Ushinsky Yaroslavl State Pedagogical University, Yaroslavl, Russia

³ Grodno State Medical University, Grodno, Republic of Belarus

Glaucoma is the leading cause of irreversible blindness. Its leading symptom and the most important initial link of the disease pathogenesis is represented by an increase of intraocular pressure (IOP). Decrease of IOP is a basic notion in the therapy of glaucoma. Drug-induced therapy is currently the most widely spread initial intervention to decrease IOP. Prostaglandin analogues are referred to the basic group of pharmacotherapeutic agents, because they are the most effective and well tolerated. Beta-blocking agents are selected as an alternative. Other medicinal products to treat glaucoma include inhibitors of carbonic anhydrase for systemic (acetazolamide and methazolamide) and local (dorzolamide and brinzolamide) use. Systemic inhibitors of carbonic anhydrase are, on the one hand, more active than non-systemic medicinal preparations, and, on the other hand, have numerous side effects which are not safe for humans. Thus, medicinal preparations for local use are most frequently applied in the therapy of glaucoma. If necessary, they are combined with beta-blocking agents or alpha-adrenergic agonists.

Keywords: glaucoma, intraocular pressure, carbonic anhydrase inhibitors

Author contribution: Strakhov VV — concept and design development, article editing; Korsakov MK — responsibility for proper presentation of issues related to data validity and integrity of all parts; Fedorov VN — concept and design development, article editing, responsibility for proper presentation of issues related to data validity and integrity of all parts; Vdovichenko VP — data collection, analysis and interpretation, primary writing; Shetnev AA — writing, language design of the text, compliance with scientific terms; Popova AA — drawing up the list of references by the order of references in the text; Volkhin NN — compliance with requirements to design of the article intended for publication.

✉ **Correspondence should be addressed:** Mikhail K. Korsakov
ul. Technoparkovaya, 11/2, Yaroslavl, 150030, Russia; mkkors@mail.ru

Received: 16.01.2023 **Accepted:** 21.02.2023 **Published online:** 30.03.2023

DOI: 10.24075/medet.2023.001

ИНГИБИТОРЫ КАРБОНАГИДРАЗЫ В ТЕРАПИИ ГЛАУКОМЫ

В. В. Страхов¹, М. К. Корсаков² ✉, В. Н. Федоров^{1,2}, В. П. Вдовиченко³, А. А. Шетнев², А. А. Попова², Н. Н. Вольхин^{1,2}

¹ Ярославский государственный медицинский университет, Ярославль, Россия

² Ярославский государственный педагогический университет им. К. Д. Ушинского, Ярославль, Россия

³ Гродненский государственный медицинский университет, Гродно, Республика Беларусь

Глаукома является ведущей причиной необратимой слепоты. Ее ведущий симптом и важнейшее начальное звено патогенеза заболевания — повышение внутриглазного давления (ВГД), а его снижение — это базисное понятие в терапии глаукомы. Медикаментозная терапия в настоящее время является наиболее распространенным начальным вмешательством для снижения ВГД. Основной группой фармакотерапевтических средств являются аналоги простагландинов, поскольку они наиболее эффективны и хорошо переносятся. В качестве их альтернативы выбираются бета-адреноблокаторы. Ко второму ряду средств для лечения глаукомы относятся ингибиторы карбоангидразы для системного (ацетазоламид и метазоламид) и местного (дорзоламид и бринзоламид) применения. Системные ингибиторы карбоангидразы, с одной стороны, более активны, чем несистемные препараты, а с другой — обладают многочисленными и небезопасными для человека побочными эффектами. Вследствие этого наиболее часто в терапии глаукомы используются препараты для местного применения, которые, при необходимости, комбинируются с бета-адреноблокаторами или альфа-адреномиметиками.

Ключевые слова: глаукома, внутриглазное давление, ингибиторы карбоангидразы

Вклад авторов: В. В. Страхов — разработка концепции и дизайна, редактирование статьи; М. К. Корсаков — ответственность за надлежащее изложение вопросов, связанное с достоверностью данных и целостностью всех частей; В. Н. Федоров — разработка концепции и дизайна, редактирование статьи, ответственность за надлежащее изложение вопросов, связанное с достоверностью данных и целостностью всех частей; В. П. Вдовиченко — сбор, анализ и интерпретация материала, первичное написание; А. А. Шетнев — написание, языковое оформление текста, соответствие научной терминологии; А. А. Попова — оформление списка литературы по порядку упоминания источников в тексте; Н. Н. Вольхин — соблюдение требований оформления статьи для публикации.

✉ **Для корреспонденции:** Михаил Константинович Корсаков
ул. Технопарковая, д. 11/2, г. Ярославль, 150030, Россия; mkkors@mail.ru

Статья поступила: 16.01.2023 **Статья принята к печати:** 21.02.2023 **Опубликована онлайн:** 30.03.2023

DOI: 10.24075/medet.2023.001

Glaucoma is the leading cause of irreversible blindness [1]. It unites a large group of eye diseases (about 60) with the following features: intraocular pressure (IOP) constantly or periodically exceeds the tolerant (individually tolerant) level; characteristic damage to the optic nerve head and ganglion cells of the retina (glaucoma optic neuropathy — GON), disturbances of visual functions typical of glaucoma are developed.

According to the World Health Organization (WHO), a number of patients with glaucoma around the world varies from 60.5 to 105 mil. people. Meanwhile it is expected that a number of patients will be increased by 10 mil. during the next 10 years. In Russia, over 1 mil. of patients with glaucoma have been revealed. However, a true number of patients is twice as high [Clinical recommendations — Primary open-angle

glaucoma — 2020 (16.02.2021) — Approved by the Ministry of Health of Russia — liter: 22, 98].

Increase of intraocular pressure (IOP) is the leading symptom of glaucoma and the most important initial link of the disease pathogenesis. Recently, the notion of 'tolerant IOP' has become increasingly common. It means the range of IOP, which is safe for this person. Tolerant IOP is not only subject to individual variations, but can also be changed throughout life and under the effect of certain general and eye diseases. Thus, the individual value of tolerant pressure can be significantly lower than the upper limit of statistically normal IOP.

Decrease in intraocular pressure (IOP) is a basic term in glaucoma therapy. In open-angle glaucoma, it is the basis of treatment, in close-angle glaucoma it is a part of complex therapy, which requires a surgery [2–4]. Currently, drug-induced therapy is the most widely spread initial intervention to decrease IOP [2–4]. The basic group of pharmacotherapeutic agents is represented by prostaglandin analogues, as they are the most effective ones (decrease of IOP by 25–33%), well tolerated and they should be instilled into an eye only once a day [2, 3, 5–8]. Ophthalmological forms of beta-blocking agents are selected as an alternative (in case of intolerance or other obstacles for indication of prostaglandins) [2, 3, 8, 9]. They result in IOP decrease by 20–25% [2]. Other agents for glaucoma treatment include carbonic anhydrase inhibitors for systemic (peroral) and local use (decrease of IOP by 20–30%), alpha2-adrenergic agonists, parasympathomimetics, and rho-kinase inhibitors [2, 3, 10, 11].

Ophthalmological agents of carbonic anhydrase inhibitors include dorzolamide (2% eye drops and a combined preparation with 0.5% timolol) and brinzolamide (1% eye suspension and a combined preparation with 0.2% brimonidine) [4]. These agents decrease IOP by 15–20% [2]. Peroral (systemic) carbonic anhydrase inhibitors are more active and represented by acetazolamide (tablets 125 and 250 mg; sustain-action tablets 500 mg) and methazolamide (tablets, 25 and 50 mg). Acetazolamide is used in an acute attack of glaucoma [4]. Today, two generations of drugs from the group of carbonic anhydrase inhibitors are distinguished. The 1st generation carbonic anhydrase inhibitors include acetazolamide and methazolamide, the 2nd generation agents involve non-systemic dorzolamide and brinzolamide.

Comparative effectiveness and tolerance of 1st and 2nd generation carbonic anhydrase inhibitors in glaucoma are reviewed in a number of studies [12–14].

As far as effectiveness of these agents go, it should be noted that acetazolamide produces a more active effect on IOP control as compared with dorzolamide. Thus, in a randomized, double-blind, placebo-controlled study of 40 people at 2 academic sites [12] acetazolamide decreased IOP by 19% in average ($P < 0.001$), whereas dorzolamide did the same by 13% ($P < 0.001$). The result was confirmed during a randomized, multi-centered, double blind, parallel cohort study with 215 patients with open-angle glaucoma or eye hypertension. Dorzolamide (2% solution TID) or acetazolamide (250 mg QID) were added to 0.5 timolol maleate ophthalmic gel-forming solution for 12 weeks [13]. Control of IOP was statistically better ($P = 0.009$) in the group of acetazolamide (0.1 ± 0.42 mm Hg) as compared with dorzolamide (1.9 ± 0.43 mm Hg).

During an earlier study involving 105 patients where acetazolamide and dorzolamide were added to timolol in a randomized fashion while treating glaucoma for 12 weeks [14], similar results were obtained: the average IOP was slightly lower (approximately by 1 mm Hg), during intake of acetazolamide it

was reduced in a more active way approximately by 1 mm Hg as compared with dorzolamide [14].

Acetazolamide reduced formation of IOP more actively as compared with dorzolamide: by 30% and 17%, respectively. The difference between the action of acetazolamide and dorzolamide was statistically significant ($P < 0.001$). When acetazolamide was added to dorzolamide, formation of intraocular liquid was additionally reduced by 16% ($P < 0.001$). In case dorzolamide was added to acetazolamide, no additional decrease of the flow was observed ($P = 0.73$) [12]. However, dorzolamide displayed a significantly better tolerance by patients as compared with acetazolamide in all three studies [13, 14].

Acetazolamide was associated with a statistically greater number of systemic adverse events than dorzolamide (dorzolamide 26%, acetazolamide 53%, $p < 0.001$) and cases of treatment discontinuation due to side effects (dorzolamide 2–8%, acetazolamide 24–25%, $p = 0.007$) [13, 14]. In the group of dorzolamide, incidence of systemic adverse reactions was reduced by 50% by week 12 but remained the same in the group of acetazolamide ($p < 0.001$) [14]. A higher rate of adverse events due to administration of acetazolamide 1st generation carbonic anhydrase inhibitors and its more frequent discontinuation were found in these studies as compared with dorzolamide [13, 14].

Thus, as far as 2nd generation agents go, they are safe enough and have obvious advantages in a clinic because they cause adverse effects to a much lesser extent [4]. Regular adverse effects of systemic inhibitors of carbonic anhydrase include paresthesia (of feet and hands), discomfort in the stomach, hypopotassemia, kidney stones and allergic reactions. In case of acetazolamide intake, stomach discomfort and paresthesia occur more frequently than in case of methazolamide [4]. With acetazolamide, very rare, but sometimes severe adverse effects are developed (acute renal insufficiency, paralytic ileus, thrombocytopenia, myopia in the highlands, and Steven-Johnson syndrome) [15–19]. Burning and tingling in the eye and such a systemic adverse effect as metallic taste in the mouth are found while using dorzolamide (more frequently) and brinzolamide (less frequently) [4].

It has become a tradition of therapeutic use of the 2nd generation carbonic anhydrase inhibitors to increase effectiveness of prostaglandins or beta-adrenal blockers. α_2 -adrenoceptor agonists are often used for this purpose apart from 2nd generation carbonic anhydrase inhibitors. An extensive meta-analysis (26 tests involving 5583 patients) was conducted to estimate effectiveness and safety of brinzolamide and dorzolamide as add-on therapy to analogs of prostaglandin or beta-blocking agents during treatment of patients with glaucoma or eye hypertension, which can't properly control IOP in monotherapy [20]. It has been shown that brinzolamide and timolol were not significantly different regarding decrease in IOP as addition to prostaglandins; equal effectiveness of administration was found during comparison with dorzolamide.

As compared with brimonidine (BID), brinzolamide caused a more significant decrease in IOP in the morning ($P < 0.0001$), but not during the rest of the day, when its effectiveness was equal to that of brimonidine (BID). When brimonidine was used thrice a day, it provided a greater effect than while taking brinzolamide TID ($P = 0.02$). The study has shown that brinzolamide, dorzolamide and timolol are similarly safe and produce no serious adverse effects.

It has been found out that brinzolamide as addition to prostaglandins or beta-adrenoblockers effectively reduced IOP in patients with refractory glaucoma or eye hypertension without causing significant adverse reactions [20].

In two studies, effectiveness of additional therapy with α_2 -adrenomimetics or 2nd generation carbonic anhydrase inhibitors combined with prostaglandin preparations has been compared [21].

163 patients with primary open-angle glaucoma, exfoliative glaucoma or eye hypertension with IOP who obtained travoprost 0.004% participated in the double-blind, three-month, randomized, multi-centered, parallel-group clinical study. The patients were randomized to obtain additional therapy with brimonidine 0.15% BID (N = 79) or brinzolamide 1% BID (N = 84). Three months of combined therapy in the group of travoprost+brimonidine was followed by a significant decrease in the average daily IOP from $21,7 \pm 0,33$ mm Hg to $18,4 \pm 0,33$ mm Hg. Decrease of IOP in both groups was significant. The intergroup difference was significant in favor of brinzolamide (P = 0.035). Authors conclude that a combination of travoprost and brinzolamide was therapeutically more effective in respect to IOP decrease as compared with a combination of travoprost and brimonidine [21].

A single-center, blind, parallel-group, randomized controlled clinical study involving 120 patients with open-angle glaucoma or eye hypertension was devoted to comparative effectiveness of brimonidine, dorzolamide and brinzolamide in relation to IOP decrease when used as an add-on therapy to prostaglandin analogues [22].

Bimatoprost, latanoprost or travoprost administered once a day belonged to prostaglandin analogues. The patients were randomized only if add-on therapy was provided: 0.15% of brimonidine tartrate (n = 41), 2% dorzolamide hydrochloride (n = 40) or 1% of brinzolamide (n = 39) were administered TID for 4 months.

RESULTS

The mean value of IOP was compared every hour at baseline in all groups. After initiation of add-on therapy, the mean IOP was significantly decreased in all examined groups of patients. However, add-on therapy was followed by a significant decrease of the mean IOP in all examined groups of patients. During this study, a mean change of IOP from baseline was greater in the group of brimonidine as compared with dorzolamide and brinzolamide (P < 0.001). Effectiveness of dorzolamide and brinzolamide was nearly the same [22].

When an effect of brinzolamide and timolol IOP on therapeutic effectiveness of latanoprost (prospective, randomized study involving 32 patients with primary open-angle glaucoma, normal tension glaucoma or eye hypertension) was compared at 12 weeks, both brinzolamide and timolol reduced IOP by 2.0 mm Hg in average with equal effectiveness (P < 0.01). The medicinal products had equal safety among patients [23].

In another perspective, 8-week, open-label, crossover clinical study (26 patients with glaucoma or eye hypertension) a significantly better therapeutic effectiveness of latanoprost was obtained with add-on of 1% of brinzolamide (TID) or 0.5% of gel-forming solution of timolol (once every morning). However, only add-on therapy with brinzolamide could significantly reduce IOP at night [24].

2nd generation carbonic anhydrase inhibitors are frequently used with adrenergic blocking agents and most frequently timolol. In this case, equal therapeutic effectiveness of brinzolamide and dorzolamide is displayed [25]. 1% brinzolamide was equally effective when administered BID and TID producing an average daily reduction of IOP as compared with baseline within the range of 13.2–21.8% [25]. Thus, a dose

given twice a day is one of the least expensive add-ons to therapy with beta-blockers in glaucoma and is associated with lesser direct medical costs as compared with dorzolamide [25].

Another study was related to comparative cost of treatment with brinzolamide and dorzolamide in France, Italy, Portugal and Spain among patients with eye hypertension or primary open-angle glaucoma [26]. The following results were obtained: provided as monotherapy BID or TID, brinzolamide was as effective as dorzolamide TID. Brinzolamide BID and timolol was as effective as a combination of dorzolamide and timolol BID. Direct medical expenses for patients with brinzolamide were lower as compared with those who were administered dorzolamide. The authors concluded that brinzolamide was a more saving alternative to dorzolamide [26].

In 12-month, double-blind, randomized, multi-centered, parallel-group study (34 institutions and 523 patients with open-angle glaucoma or eye hypertension), safety and effectiveness of 2% solution of dorzolamide were compared (TID) with those of 0.5% maleate timolol and 0.5% of betaxolol hydrochloride (BID) [27]. Effect obtained during add-on of dorzolamide to treatment of patients with non-adequate eye hypotensive effectiveness and effect from adding timolol to treatment with dorzolamide were assessed as well.

The following results were obtained during the study: the mean percentage of IOP decrease was obtained at one year of administration of 2% dorzolamide, 0.5% of timolol and 0.5% of betaxolol and amounted to 23%, 25% and 21%, respectively. The authors made a conclusion that an effective decrease of IOP during the course of treatment for up to 1 year when 2% dorzolamide was administered TID was compared with that of 0.5% of betaxolol taken BID [27].

A randomized, open-label, parallel-group study was conducted at 5 sites of Greece to compare a decrease of IOP when dorzolamide was added to timolol [28]. The study included 148 patients with not properly controlled open-angle or pseudoexfoliative glaucoma or eye hypertension resulting in an additive effect of decreased daily IOP from dorzolamide among patients obtaining timolol. At three months, a daily IOP was decreased by 20% in the group of dorzolamide plus timolol. At 3 months, the mean daily decrease of IOP by -4.44 mm Hg (P < 0.001) was estimated with the least square method [28].

Similar results were obtained in a study with 17 patients (timolol plus dorzolamide BID). At three months of treatment, IOP was decreased by 15.6% [29].

A retrospective study of an effect of dorzolamide and brinzolamide on the eye function (mainly field of vision) in open-angle glaucoma and eye hypertension was conducted [30]. No significant protection effect in relation to occurrence of glaucoma in patients with eye hypertension was found during the European Glaucoma Prevention Study where dorzolamide was compared with placebo. In two other long-term studies, superiority of dorzolamide add-on over monotherapy with timolol and superiority of a combination of dorzolamide and timolol over brinzolamide and timolol in relation to ocular blood flow improvement (retrobulbar color Doppler ultrasonography — CDI values) and preservation of the field of vision in patients with glaucoma found 4–5 years ago were reported [30].

Fixed combinations of various agents reducing IOP have acquired important relevance for treatment of open-angle glaucoma. Fixed combinations reduce a number of daily instillations, increasing treatment compliance and reducing an effect of preservatives on the eye [31]. All available publications in relation to fixed combinations of dorzolamide or brinzolamide (in the pharmaceutical market, they are represented by preparations in combination with such a beta-blocker

as timolol) can be conditionally divided into the following groups: 1) studies of effectiveness and side effects of a fixed combination as compared with monotherapy with separate components; 2) comparison of effectiveness and adverse effects of dorzolamide+timolol and brinzolamide+timolol; 3) comparison of dorzolamide+timolol with representatives of other groups (brimonidine+timolol and latanoprost).

Predictably, combinations of dorzolamide/timolol and brimonidine/timolol were more effective than monotherapy with separate components of these combinations [32–37]. Meanwhile, effective decrease of IOP was similar with both combinations [31, 38]. A combination of timolol and brinzolamide was tolerated better than timolol plus dorzolamide due to less eye irritation by brinzolamide [31, 38].

Effectiveness and tolerance of dorzolamide/timolol and brimonidine/timolol were approximately similar. It indirectly testifies to almost equal clinical effectiveness of carbonic anhydrase inhibitors and alpha2-adrenergic agonists [39]. Dorzolamide/timolol is as effective in relation to IOP decrease as latanoprost therapy [40]. Meanwhile, latanoprost was better tolerated by patients. The study confirms validity of clinical recommendations to use prostaglandin preparations in glaucoma as drugs of choice [2, 3].

Pharmaceutical characteristics of combinations are paid attention to as well. Fixed combinations of dorzolamide/timolol with preservative (DTFC) and DTFC without preservatives (PF)

were compared [41]. It is found out that PF DTFC has equivalent effectiveness to that of DTFC. Due to improved tolerance and adherence, it has advantages in patients with glaucoma who suffer from ocular surface diseases [41].

CONCLUSION

In treatment of glaucoma, carbonic anhydrase inhibitors have rather high clinical effectiveness in IOP decrease and (mainly, 2nd generation carbonic anhydrase inhibitors) low risk of serious side effects. They can be used as alternative agents when it is impossible to administer drugs of choice such as ophthalmic agents belonging to the group of prostaglandins or beta-blockers. When monotherapy of glaucoma with beta-blocking agents is not effective enough, fixed combinations of brinzolamide or dorzolamide and timolol are applied. Meanwhile, brinzolamide is superior to dorzolamide due to less irritation of the eye and pharmacoeconomic advantages.

The work is prepared within the state assignment of the Ministry of Education of Russia for the research project of 'Development of an innovative agent to treat open-angle glaucoma using selective inhibition of carbonic anhydrase II' (073–00109–22–02).

It is done in cooperation with the scientific department of Pharmacy Institute of the Yaroslavl State Medical University, Yaroslavl.

References

1. Tham YC, et al. Global prevalence of glaucoma and projections of glaucoma burden through 2040: a systematic review and meta-analysis. *Ophthalmology*. 2014, 121: 2081–2090.
2. Primary Open-Angle Glaucoma Preferred Practice Pattern 2020 (American Academy of Ophthalmology). Available from URL: <https://www.aao.org/preferred-practice-pattern/primary-open-angle-glaucoma-ppp>
3. NICE guideline [NG81] Published: 01 November 2017. Available from URL: <https://www.nice.org.uk/guidance/ng81/chapter/Recommendations#treatment>
4. Brunton L Laurence. Goodman & Gilman's The Pharmacological Basis of Therapeutics. Laurence L. Bruce A Chabner, Randa Hilal-Dandan, Björn C Knollmann. 13th Ed, N. Y.: McGraw-Hill. 2018; 451, 1262 p.
5. Garway-Heath DF, Crabb DP, Bunce C, et al. Latanoprost for open-angle glaucoma (UKGTS): A randomised, multicentre, placebo-controlled trial. *Lancet*. 2015; 385: 1295–1304.
6. Whitson JT. Glaucoma: A review of adjunctive therapy and new management strategies. *Expert Opin Pharmacother*. 2007; 8: 3237–3249.
7. McKinnon SJ, Goldberg LD, Peeples P, et al. Current management of glaucoma and the need for complete therapy. *Am J Manag Care*. 2008;14: 20–27.
8. Li T, Lindsley K, Rouse B, et al. Comparative effectiveness of first-line medications for primary open-angle glaucoma: A systematic review and network meta-analysis. *Ophthalmology*. 2016; 123: 129–140.
9. Boland MV, Ervin AM, Friedman DS, et al. Comparative effectiveness of treatments for open-angle glaucoma: A systematic review for the U.S. Preventive Services Task Force. *Ann Intern Med*. 2013; 158: 271–279.
10. van der Valk R, Webers CA, Schouten JS, et al. Intraocular pressure-lowering effects of all commonly used glaucoma drugs: A meta-analysis of randomized clinical trials. *Ophthalmology*. 2005; 112: 1177–1185.
11. Cheng JW, Cai JP, Wei RL. Meta-analysis of medical intervention for normal tension glaucoma. *Ophthalmology*. 2009; 116: 1243–1249.
12. Maus TL, Larsson LI, McLaren JW, Brubaker RF. Comparison of dorzolamide and acetazolamide as suppressors of aqueous humor flow in humans. *Arch Ophthalmol*. 1997 Jan; 115 (1): 45–9.
13. Stewart W, Halper L, Johnson-Pratt L, Polis A, Hartenbaum D. Tolerability and efficacy of dorzolamide versus acetazolamide added to timolol. *J Ocul Pharmacol Ther*. 2002 Jun; 18(3): 211–20.
14. Hutzelmann JE, Polis AB, Michael AJ, Adamsons IA. A comparison of the efficacy and tolerability of dorzolamide and acetazolamide as adjunctive therapy to timolol. Oral to Topical CAI Study Group. *Acta Ophthalmol Scand*. 1998 Dec; 76(6): 717–22.
15. Epelde Gonzalo F, Llibre Bombardó J, Martínez Pérez J. Acetazolamide induced acute renal failure without evidence of renal obstruction. *An Med Interna*. 1998 Aug; 15 (8): 451.
16. Kodjikian L, Durand B, Burillon C, Rouberol F, Grange JD, Renaudier P. Acetazolamide-induced thrombocytopenia. *Arch Ophthalmol*. 2004 Oct; 122 (10): 1543–4.
17. Szawarski P, Hall-Thompson B. Acetazolamide-induced myopia at altitude. *Wilderness Environ Med*. 2009 Fall; 20 (3): 300–1.
18. Batke M, Cappell MS. Adynamic ileus and acute colonic pseudo-obstruction. *Med Clin North Am*. 2008 May; 92 (3): 649–70.
19. Her Y, Kil MS, Park JH, Kim CW, Kim SS. Stevens-Johnson syndrome induced by acetazolamide. *J Dermatol*. 2011 Mar; 38 (3): 272–5.
20. Yuanzhi Liu, Junyi Zhao, Xiaoyan Zhong, Qiming Wei, Yilan Huang. Efficacy and Safety of Brinzolamide as Add-On to Prostaglandin Analogues or β -Blocker for Glaucoma and Ocular Hypertension: A Systematic Review and Meta-Analysis. *Front Pharmacol*. 2019 Jun 25; 10: 679.
21. Feldman RM, Tanna AP, Gross RL, Chuang AZ, Baker L, Reynolds A, Prager TC, Additivity Study Group. Comparison of the ocular hypotensive efficacy of adjunctive brimonidine 0.15% or brinzolamide 1% in combination with travoprost 0.004%. *Ophthalmology*. 2007 Jul; 114 (7): 1248–54.
22. Bournias T, Lai J. Brimonidine tartrate 0.15%, dorzolamide hydrochloride 2%, and brinzolamide 1% compared as adjunctive therapy to prostaglandin analogs// *Ophthalmology*. 2009 Sep; 116 (9): 1719–24.
23. Katsuya Miura, Kunio Ito, Chikahiro Okawa, Kota Sugimoto, Koichi Matsunaga, Yukitaka Uji. Comparison of ocular hypotensive effect and safety of brinzolamide and timolol added to latanoprost. *J Glaucoma*. Apr-May 2008; 17 (3): 233–7.
24. Liu JH, Medeiros FA, Slight JR, Weinreb RN. Comparing diurnal and nocturnal effects of brinzolamide and timolol on intraocular

- pressure in patients receiving latanoprost monotherapy. *Ophthalmology*. 2009 Mar; 116 (3): 449–54.
25. Cvetkovic R, Perry C. Brinzolamide: a review of its use in the management of primary open-angle glaucoma and ocular hypertension. *Drugs Aging*. 2003; 20 (12): 919–47.
 26. Rouland JF, Le Pen C, Gouveia Pinto C, Berto P, Berdeaux G. Cost-minimisation study of dorzolamide versus brinzolamide in the treatment of ocular hypertension and primary open-angle glaucoma: in four European countries. *Pharmacoeconomics*. 2003; 21 (3): 201–13.
 27. Strahlman E, Tipping R, Vogel R. A double-masked, randomized 1-year study comparing dorzolamide (Trusopt), timolol, and betaxolol. International Dorzolamide Study Group. *Arch Ophthalmol*. 1995 Aug; 113(8): 1009–16.
 28. Petounis A, Mylopoulos N, Kandarakis A, Andreanos D, Dimitrakoulis N. Comparison of the additive intraocular pressure-lowering effect of latanoprost and dorzolamide when added to timolol in patients with open-angle glaucoma or ocular hypertension: a randomized, open-label, multicenter study in Greece. *J Glaucoma*. 2001 Aug; 10 (4): 316–24.
 29. Polo V, Larrosa JM, Gomez ML, Pablo L, Honrubia FM. Latanoprost versus combined therapy with timolol plus dorzolamide: IOP-lowering effect in open-angle glaucoma. *Acta Ophthalmol Scand*. 2001 Feb; 79 (1): 6–9.
 30. Gugleta K. Topical carbonic anhydrase inhibitors and visual function in glaucoma and ocular hypertension. *Curr Med Res Opin*. 2010.
 31. Holló G, Bozkurt B, Irkeç M. Brinzolamide/timolol fixed combination: a new ocular suspension for the treatment of open-angle glaucoma and ocular hypertension. *Expert Opin Pharmacother*. 2009 Aug; 10 (12): 2015–24.
 32. Frampton JE, Perry CM. Topical dorzolamide 2%/timolol 0.5% ophthalmic solution: a review of its use in the treatment of glaucoma and ocular hypertension. *Drugs Aging*. 2006; 23 (12): 977–95.
 33. Katz G, Dubiner H, Samples J, Vold S, Sall K. Three-month randomized trial of fixed-combination brinzolamide, 1%, and brimonidine, 0.2%. *JAMA Ophthalmol*. 2013 Jun; 131 (6): 724–30.
 34. Realini T, Nguyen QH, Katz G, Dubiner H. Fixed-combination brinzolamide 1%/brimonidine 0.2% vs monotherapy with brinzolamide or brimonidine in patients with open-angle glaucoma or ocular hypertension: results of a pooled analysis of two phase 3 studies. *Eye (Lond)*. 2013 Jul; 27 (7): 841–7.
 35. Quang H, Nguyen, Matthew G. McMenemy, Tony Realini, Jess T. Whitson, Stephen M. Goode. Phase 3 Randomized 3-Month Trial with an Ongoing 3-Month Safety Extension of Fixed-Combination Brinzolamide 1%/Brimonidine 0.2%. *J Ocul Pharmacol Ther*. 2013 Apr; 29 (3): 290–297.
 36. Boyle JE, Ghosh K, Gieser DK, Adamsons IA. A randomized trial comparing the dorzolamide-timolol combination given twice daily to monotherapy with timolol and dorzolamide. *Ophthalmology*. 1999 Dec; 106 (12 Suppl): 10–6.
 37. Ormrod D, McClellan K. Topical dorzolamide 2%/timolol 0.5%: a review of its use in the treatment of open-angle glaucoma. *Drugs Aging*. 2000 Dec; 17 (6): 477–96.
 38. Manni G, Denis Ph, Chew P, Sharpe ED, Orengo-Nania S, Coote MA, Laganovska G, Volksone L, Zeyen T, Filatori I, James J, Aung T. The safety and efficacy of brinzolamide 1%/timolol 0.5% fixed combination versus dorzolamide 2%/timolol 0.5% in patients with open-angle glaucoma or ocular hypertension. *J Glaucoma*. Apr-May 2009; 18 (4): 293–300.
 39. Hatanaka M, Grigera DE, Barbosa WL, Jordao M, Susanna R Jr. An eight-week, multicentric, randomized, interventional, open-label, phase 4, parallel comparison of the efficacy and tolerability of the fixed combination of timolol maleate 0.5%/brimonidine tartrate 0.2% versus fixed combination of timolol maleate 0.5%/dorzolamide 2% in patients with elevated intraocular pressure. *J Glaucoma*. 2008 Dec; 17 (8): 674–9.
 40. Remo Susanna Jr, Wang-Pui Sheu, Latin American Glaucoma Society. Comparison of latanoprost with fixed-combination dorzolamide and timolol in adult patients with elevated intraocular pressure: an eight-week, randomized, open-label, parallel-group, multicenter study in Latin America. *Clin Ther*. 2004 May; 26 (5): 755–68.
 41. Konstas AG, Schmetterer L, Katsanos A, Hutnik CM, Holló G, Quaranta L, Teus M, Uusitalo H, Pfeiffer N, Katz G. Dorzolamide/Timolol Fixed Combination: Learning from the Past and Looking Toward the Future. *Adv Ther*. 2021 Jan; 38 (1): 24–51.

Литература

1. Tham YC, et al. Global prevalence of glaucoma and projections of glaucoma burden through 2040: a systematic review and meta-analysis. *Ophthalmology*. 2014, 121: 2081–2090.
2. Primary Open-Angle Glaucoma Preferred Practice Pattern 2020 (American Academy of Ophthalmology). Available from URL: <https://www.aao.org/preferred-practice-pattern/primary-open-angle-glaucoma-ppp>
3. NICE guideline [NG81] Published: 01 November 2017. Available from URL: <https://www.nice.org.uk/guidance/ng81/chapter/Recommendations#treatment>
4. Brunton L Laurence. Goodman & Gilman's The Pharmacological Basis of Therapeutics. Laurence L. Bruce A Chabner, Randa Hilal-Dandan, Björn C Knollmann. 13th Ed, N. Y.: McGraw-Hill. 2018; 451, 1262 p.
5. Garway-Heath DF, Crabb DP, Bunce C, et al. Latanoprost for open-angle glaucoma (UKGTS): A randomised, multicentre, placebo-controlled trial. *Lancet*. 2015; 385: 1295–1304.
6. Whitson JT. Glaucoma: A review of adjunctive therapy and new management strategies. *Expert Opin Pharmacother*. 2007; 8: 3237–3249.
7. McKinnon SJ, Goldberg LD, Peeples P, et al. Current management of glaucoma and the need for complete therapy. *Am J Manag Care*. 2008;14: 20–27.
8. Li T, Lindsley K, Rouse B, et al. Comparative effectiveness of first-line medications for primary open-angle glaucoma: A systematic review and network meta-analysis. *Ophthalmology*. 2016; 123: 129–140.
9. Boland MV, Ervin AM, Friedman DS, et al. Comparative effectiveness of treatments for open-angle glaucoma: A systematic review for the U.S. Preventive Services Task Force. *Ann Intern Med*. 2013; 158: 271–279.
10. van der Valk R, Webers CA, Schouten JS, et al. Intraocular pressure-lowering effects of all commonly used glaucoma drugs: A meta-analysis of randomized clinical trials. *Ophthalmology*. 2005; 112: 1177–1185.
11. Cheng JW, Cai JP, Wei RL. Meta-analysis of medical intervention for normal tension glaucoma. *Ophthalmology*. 2009; 116: 1243–1249.
12. Maus TL, Larsson LI, McLaren JW, Brubaker RF. Comparison of dorzolamide and acetazolamide as suppressors of aqueous humor flow in humans. *Arch Ophthalmol*. 1997 Jan; 115 (1): 45–9.
13. Stewart W, Halper L, Johnson-Pratt L, Polis A, Hartenbaum D. Tolerability and efficacy of dorzolamide versus acetazolamide added to timolol. *J Ocul Pharmacol Ther*. 2002 Jun; 18(3): 211–20.
14. Hutzelmann JE, Polis AB, Michael AJ, Adamsons IA. A comparison of the efficacy and tolerability of dorzolamide and acetazolamide as adjunctive therapy to timolol. Oral to Topical CAI Study Group. *Acta Ophthalmol Scand*. 1998 Dec; 76(6): 717–22.
15. Epelde Gonzalo F, Llibre Bombardó J, Martínez Pérez J. Acetazolamide induced acute renal failure without evidence of renal obstruction. *An Med Interna*. 1998 Aug; 15 (8): 451.
16. Kodjikian L, Durand B, Burillon C, Rouberol F, Grange JD, Renaudier P. Acetazolamide-induced thrombocytopenia. *Arch Ophthalmol*. 2004 Oct; 122 (10): 1543–4.
17. Szawarski P, Hall-Thompson B. Acetazolamide-induced myopia at altitude. *Wilderness Environ Med*. 2009 Fall; 20 (3): 300–1.
18. Batke M, Cappell MS. Adynamic ileus and acute colonic pseudo-obstruction. *Med Clin North Am*. 2008 May; 92 (3): 649–70.
19. Her Y, Kil MS, Park JH, Kim CW, Kim SS. Stevens-Johnson syndrome induced by acetazolamide. *J Dermatol*. 2011 Mar; 38 (3): 272–5.

20. Yuanzhi Liu, Junyi Zhao, Xiaoyan Zhong, Qiming Wei, Yilan Huang. Efficacy and Safety of Brinzolamide as Add-On to Prostaglandin Analogues or β -Blocker for Glaucoma and Ocular Hypertension: A Systematic Review and Meta-Analysis. *Front Pharmacol*. 2019 Jun 25; 10: 679.
21. Feldman RM, Tanna AP, Gross RL, Chuang AZ, Baker L, Reynolds A, Prager TC, Additivity Study Group. Comparison of the ocular hypotensive efficacy of adjunctive brimonidine 0.15% or brinzolamide 1% in combination with travoprost 0.004%. *Ophthalmology*. 2007 Jul; 114 (7): 1248–54.
22. Bournias T, Lai J. Brimonidine tartrate 0.15%, dorzolamide hydrochloride 2%, and brinzolamide 1% compared as adjunctive therapy to prostaglandin analogs// *Ophthalmology*. 2009 Sep; 116 (9): 1719–24.
23. Katsuya Miura, Kunio Ito, Chikahiro Okawa, Kota Sugimoto, Koichi Matsunaga, Yukitaka Uji. Comparison of ocular hypotensive effect and safety of brinzolamide and timolol added to latanoprost. *J Glaucoma*. Apr-May 2008; 17 (3): 233–7.
24. Liu JH, Medeiros FA, Slight JR, Weinreb RN. Comparing diurnal and nocturnal effects of brinzolamide and timolol on intraocular pressure in patients receiving latanoprost monotherapy. *Ophthalmology*. 2009 Mar; 116 (3): 449–54.
25. Cvetkovic R, Perry C. Brinzolamide: a review of its use in the management of primary open-angle glaucoma and ocular hypertension. *Drugs Aging*. 2003; 20 (12): 919–47.
26. Rouland JF, Le Pen C, Gouveia Pinto C, Berto P, Berdeaux G. Cost-minimisation study of dorzolamide versus brinzolamide in the treatment of ocular hypertension and primary open-angle glaucoma: in four European countries. *Pharmacoeconomics*. 2003; 21 (3): 201–13.
27. Strahlman E, Tipping R, Vogel R. A double-masked, randomized 1-year study comparing dorzolamide (Trusopt), timolol, and betaxolol. *International Dorzolamide Study Group*. *Arch Ophthalmol*. 1995 Aug; 113(8): 1009–16.
28. Petounis A, Mylopoulos N, Kandarakis A, Andreanos D, Dimitrakoulis N. Comparison of the additive intraocular pressure-lowering effect of latanoprost and dorzolamide when added to timolol in patients with open-angle glaucoma or ocular hypertension: a randomized, open-label, multicenter study in Greece. *J Glaucoma*. 2001 Aug; 10 (4): 316–24.
29. Polo V, Larrosa JM, Gomez ML, Pablo L, Honrubia FM. Latanoprost versus combined therapy with timolol plus dorzolamide: IOP-lowering effect in open-angle glaucoma. *Acta Ophthalmol Scand*. 2001 Feb; 79 (1): 6–9.
30. Gugleta K. Topical carbonic anhydrase inhibitors and visual function in glaucoma and ocular hypertension. *Curr Med Res Opin*. 2010.
31. Holló G, Bozkurt B, Irkec M. Brinzolamide/timolol fixed combination: a new ocular suspension for the treatment of open-angle glaucoma and ocular hypertension. *Expert Opin Pharmacother*. 2009 Aug; 10 (12): 2015–24.
32. Frampton JE, Perry CM. Topical dorzolamide 2%/timolol 0.5% ophthalmic solution: a review of its use in the treatment of glaucoma and ocular hypertension. *Drugs Aging*. 2006; 23 (12): 977–95.
33. Katz G, Dubiner H, Samples J, Vold S, Sall K. Three-month randomized trial of fixed-combination brinzolamide, 1%, and brimonidine, 0.2%. *JAMA Ophthalmol*. 2013 Jun; 131 (6): 724–30.
34. Realini T, Nguyen QH, Katz G, Dubiner H. Fixed-combination brinzolamide 1%/brimonidine 0.2% vs monotherapy with brinzolamide or brimonidine in patients with open-angle glaucoma or ocular hypertension: results of a pooled analysis of two phase 3 studies. *Eye (Lond)*. 2013 Jul; 27 (7): 841–7.
35. Quang H, Nguyen, Matthew G. McMenemy, Tony Realini, Jess T. Whitson, Stephen M. Goode. Phase 3 Randomized 3-Month Trial with an Ongoing 3-Month Safety Extension of Fixed-Combination Brinzolamide 1%/Brimonidine 0.2%. *J Ocul Pharmacol Ther*. 2013 Apr; 29 (3): 290–297.
36. Boyle JE, Ghosh K, Gieser DK, Adamsons IA. A randomized trial comparing the dorzolamide-timolol combination given twice daily to monotherapy with timolol and dorzolamide. *Ophthalmology*. 1999 Dec; 106 (12 Suppl): 10–6.
37. Ormrod D, McClellan K. Topical dorzolamide 2%/timolol 0.5%: a review of its use in the treatment of open-angle glaucoma. *Drugs Aging*. 2000 Dec; 17 (6): 477–96.
38. Manni G, Denis Ph, Chew P, Sharpe ED, Orengo-Nania S, Coote MA, Laganovska G, Volkson L, Zeyen T, Filatori I, James J, Aung T. The safety and efficacy of brinzolamide 1%/timolol 0.5% fixed combination versus dorzolamide 2%/timolol 0.5% in patients with open-angle glaucoma or ocular hypertension. *J Glaucoma*. Apr-May 2009; 18 (4): 293–300.
39. Hatanaka M, Grigera DE, Barbosa WL, Jordao M, Susanna R Jr. An eight-week, multicentric, randomized, interventional, open-label, phase 4, parallel comparison of the efficacy and tolerability of the fixed combination of timolol maleate 0.5%/brimonidine tartrate 0.2% versus fixed combination of timolol maleate 0.5%/dorzolamide 2% in patients with elevated intraocular pressure. *J Glaucoma*. 2008 Dec; 17 (8): 674–9.
40. Remo Susanna Jr, Wang-Pui Sheu, Latin American Glaucoma Society. Comparison of latanoprost with fixed-combination dorzolamide and timolol in adult patients with elevated intraocular pressure: an eight-week, randomized, open-label, parallel-group, multicenter study in Latin America. *Clin Ther*. 2004 May; 26 (5): 755–68.
41. Konstas AG, Schmetterer L, Katsanos A, Hutnik CM, Holló G, Quaranta L, Teus M, Uusitalo H, Pfeiffer N, Katz G. Dorzolamide/Timolol Fixed Combination: Learning from the Past and Looking Toward the Future. *Adv Ther*. 2021 Jan; 38 (1): 24–51.