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Topical carbonic anhydrase inhibitors and glaucoma in 2021: where do we stand?

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Abstract

Carbonic anhydrase inhibitors (CAIs) have been used for many decades in the treatment of glaucoma. Systemic CAIs were an early treatment option to lower intraocular pressure by reducing aqueous humour production; however, frequent side effects including polyuria and paresthesia contributed to the eventual development of topical CAIs. As topical drug development evolved over time, prostaglandin analogues and beta-blockers have become the gold standard of glaucoma therapies. Although prescribed less often than other classes of topical glaucoma therapies, topical CAIs continue to be used in combination therapies with beta-blockers and alpha agonists. Topical CAIs have also been demonstrated to alter biomarkers of ocular haemodynamics, which have relevance in glaucoma. The purpose of this review is to review and summarise the current state of topical CAI prescribing trends, known efficacy and suggested mechanisms and potential influence on ocular haemodynamics for the future of glaucoma management.

INTRODUCTION

Glaucoma is a multifactorial disease characterised by progressive deterioration of the optic nerve and associated visual field loss. Open-angle glaucoma (OAG) is the most common form of the disease, being a leading cause of irreversible blindness in all countries.[1]

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Currently, the only modifiable risk factor of this disease is intraocular pressure (IOP), which has been associated with disease progression and visual field loss. While lowering IOP can slow the disease progression also in subjects with IOP considered within the normal range, treating an elevated IOP does not halt disease progression in all patients. Regardless, approved treatments for OAG have been solely focused on lowering IOP through pharmaceutical or surgical intervention and no other approach to glaucoma has yet proven effective. Topical IOP-lowering therapies include carbonic anhydrase inhibitors (CAIs), alpha agonists, prostaglandin analogues, cholinergic agonists and beta-blockers with others in various stages of development.

CAIs are among the oldest agents in use for the treatment of OAG with reports demonstrating the efficacy of acetazolamide in lowering IOP as early as 1954.[2 3] While systemic CAIs such as acetazolamide and methazolamide are capable of reducing IOP in glaucoma patients, their use is burdened by significant side effects including paresthesia, diuretic effect, metabolic acidosis, electrolyte abnormalities, nausea and weakness.[4] Additionally, since these drugs are sulfa compounds, they are contraindicated in those with an allergy. Topical CAIs including dorzolamide (Trusopt) and brinzolamide (Azopt) were developed to mitigate systemic side effects through local administration and were both approved in the mid-1990s for the management of OAG. They have since become a mainstay class of drugs with popular formulations prepared in combination with other IOP-lowering medications including dorzolamide–timolol (Cosopt), brinzolamide–timolol (Azarga), and brinzolamide–brimonidine (Simbrinza).[5]

The development of several new classes of glaucoma medications has significantly altered the use of topical CAIs over the past two decades, yet they are still frequently prescribed across the world in glaucoma management. This review will, therefore, evaluate current prescribing trends of CAIs and examine their mechanistic influence on IOP, ocular haemodynamics and glaucomatous progression.

MATERIALS AND METHODS

Relevant literature with the search terms CAI, methazolamide, acetazolamide, dorzolamide, brinzolamide, Cosopt, Azopt, Azarga, Simbrinza and carbonic anhydrase were reviewed through 21 April 2021 on PubMed, Medline and associated digital databases. Reference lists of relevant articles were also searched and cross-referenced for other relevant articles on CAI and glaucoma.

Mechanism of CAIs

Chemically, CAIs reduce IOP by suppressing aqueous humour production at the ciliary bodies through the prevention of the interconversion of carbon dioxide (CO_2) and carbonic acid which freely dissociates into bicarbonate anions and protons.[2–5] Bicarbonate is thought to influence fluid transport by a pH-dependent sodium transport.[6] Additionally, studies have shown CAIs to affect ocular haemodynamics by directly reducing the resistance of vessels and thus increasing blood flow velocities, restoring proper circulation.[7]

The increase in local tissue CO_2 concentrations by CAIs is known to cause vascular dilation, specifically in cerebral tissue, and has been used when testing for vasodilative reserve potential.[8–10] This effect has been theorised to arise from local CO_2 retention and/or reduced local tissue pH, resulting in vasodilation and increased blood flow in the retinal and choroidal circulation.[10–13] Another mechanism has been suggested by which dorzolamide and acetazolamide dilate retinal vasculature independent of CAI.[14] Previous studies have implicated blood flow abnormalities as a contributing factor in the development of glaucoma[15]; thus, the ability of CAIs to increase flow has been suggested to potentially provide an additional benefit in the management of disease progression.[16–20]

Emergence of topical CAIs

Today, systemic CAIs including acetazolamide and methazolamide are still used prior to ophthalmic surgery and during acute IOP spikes.[21] Specifically, acetazolamide and methazolamide accounted for 0.5% and 0.2%, respectively, of all Medicare claims for glaucoma medications in 2015.[22] However, for chronic control of IOP, physicians have increasingly moved toward topical CAIs (ie, dorzolamide and brinzolamide) given the relatively high incidence of side effects associated with the use of systemic CAIs.[4] Topical CAIs have been shown to significantly decrease IOP in multiple studies[23–27] and are typically associated with a 15%–20% drop in IOP with potential side effects limited to allergic dermatitis/conjunctivitis, corneal oedema, keratitis and metallic taste.[28 29] While topical medications do have fewer side effects, they also require penetration of their compounds through the anterior ocular surface to reach a critical concentration in the ocular milieu, and therefore, may have reduced capacity to lower IOP with one study in rabbits[30] and one in humans[31] supporting this theory. Additionally, studies have found acetazolamide to have a similar or slightly stronger IOP-lowering effect in comparison to dorzolamide[32–34]; however, when combined no additive effect was demonstrated.[35] Relative contraindications for systemic and topical CAIs may include worsening corneal oedema,[36 37] a history of renal stones,[38] pregnancy[39] or sickle cell disease.[40 41] Additionally, while generally tolerated, the most common reason for intolerance to topical CAIs is ocular discomfort (burning and stinging) following administration, however, several studies show brinzolamide to be more tolerated than dorzolamide in this regard.[42–45]

Chemical composition, pharmacokinetics and pharmacodynamics of CAIs

The systemic CAIs, methazolamide and acetazolamide, are heterocyclic sulfonamide drugs and represent the first generation of clinically used CAIs. They are very strong inhibitors of most isoforms of carbonic anhydrase. Their broad side effect profile can be attributed to their indiscriminate inhibition of carbonic anhydrases throughout the body with a host of CA isozymes abundant in nearly every organ.[46] While topical administration of these first generation CAIs was attempted, it was found these drugs were unable to reach the ciliary processes likely due to an inability to penetrate the cornea.[47] The second generation of CAIs, dorzolamide and brinzolamide, were water-soluble and capable of penetrating the cornea and ocular milieu, allowing for topical administration and reducing the side effects associated with systemic administration.[26–41 46–49] Nonetheless, topical CAIs were found to lower IOP to a lesser degree than systemic formulations. The decreased ocular hypotensive effect of topical versus systemic CAIs is attributed to their higher IC(50) for the carbonic

anhydrase isoenzymes CA-II and CA-IV, which are thought to be those most responsible for aqueous humour production.[5 48]

IOP reduction as a measure of the effectiveness of CAIs

IOP reduction, as the only modifiable risk factor for the treatment of OAG, is used as a surrogate outcome to quantify intervention effectiveness.[50 51] A 2016 systematic review and meta-analysis by Li *et al* compared the effectiveness of first-line glaucoma medications for IOP reduction found that, when compared with brinzolamide, dorzolamide had more IOP-lowering capability with a mean difference of 0.58 mm Hg.[24] The group also ranked dorzolamide 11th and brinzolamide 12th for their ability to reduce IOP using a network meta-analysis of fourteen glaucoma medications. In order, they were less effective than bimatoprost, latanoprost, travoprost, levobunolol, tafluprost, timolol, brimonidine, carteolol, levobetaxolol and apraclonidine but were more effective than betaxolol and unoprostone. A compendium of studies demonstrating IOP reduction among topical CAIs can be found in table 1.

While topical CAIs may be less effective than other agents at reducing IOP, several factors are often considered in determining a patient's treatment plan including side effects, cost, availability and safety. For instance, prostaglandins are often considered the best performing medications but have been associated with eyelash lengthening and iris colour changes, while beta-blockers, often the most-prescribed drugs due to low cost, can induce bronchospasm and bradycardia in some patients.[4 52 53] CAIs themselves have potential significant side effects and the relative contraindications should be considered on an individual basis. Additionally, CAIs should generally be avoided in patients with sickle cell disease as they are thought to contribute to sickling. The associated risk may be partially mitigated with topical formulations (except in the case of hyphema) as well as methazolamide, given its lower risk of metabolic acidosis compared with acetazolamide.[40 41]

Effect of topical CAIs on visual function

In a 2010 review of CAI trials on visual function, all but three studies (n=23) showed topical CAIs had no effect on visual function.[54] Two studies showed some improvement in contrast sensitivity,[55 56] and one open-label retrospective no-control-group study with dorzolamide found a slight improvement in visual field indices.[57] Notably, few studies include visual field assessment as a reported outcome. A large placebo-controlled trial published in 2005 failed to detect any significant protective effect of dorzolamide on preventing disease progression in glaucoma suspects with ocular hypertension despite a 15%–22% reduction in IOP.[23] No study has performed a direct comparison between CAIs for the impact on visual function. While the aforementioned studies do indicate a lack of significant changes in visual field indices, this review is limited by the current practice of using IOP reduction as the only established variable for the prevention of glaucomatous visual field changes.[50 51]

Prescribing trends of CAIs

In the medical management of glaucoma, topical CAIs such as dorzolamide and brinzolamide are typically dosed as one drop three times daily of a 2% and 1% solution,

respectively.[58 59] A study was recently published by Priluck *et al* which investigated the prescribing trends of glaucoma drugs in the USA based on publicly available data from 2015 Medicare Part D.[22] Of the 36 glaucoma drugs included in this study, CAIs as single agents comprised 5.2% of all claims, and combination agents dorzolamide–timolol and brinzolamide–brimonidine together represented 9.7% of all claims. Among CAIs prescribed by ophthalmologists, dorzolamide represented 51.6% of claims, and dorzolamide–timolol represented 56.3% of all combination medications. Regarding other medications, prostaglandin analogues were by far the most frequently prescribed drugs, with latanoprost and bimatoprost representing 36.5% and 10.6% of all claims, respectively, followed by timolol formulations at 11.2%. Notably, these data represent only Medicare claims and are not comprehensive of the American healthcare system for which no central database is available. A study published in 2012 that analysed system-wide data from the national health service in England found single-agent topical CAIs represented 12.3% of all claims and brinzolamide represented 74.6% of all CAI claims.[60] Another study derived from six major Chinese cities between 2013 and 2017 found nearly 16% of all claims were for CAIs.[61] A recent global cost analysis of glaucoma drugs found topical CAIs to be generally costlier than beta-blockers but less expensive than prostaglandin analogues.[53]

Regarding the equivalence of generic and brand-name topical CAIs, the data available is scant. A prospective study by Kim *et al* demonstrated no statistically significant difference between generic dorzolamide–timolol and Cosopt in IOP limiting capacity.[62] Notably, the Food and Drug Administration (FDA) does not require strict demonstration of human bioequivalence and/or therapeutic studies for the approval of generic topical ophthalmic drugs, perhaps explaining this paucity of data. Nonetheless, among topical CAIs prescribed in the US in 2015, 99.9% of all Medicare claims for dorzolamide and 97.4% for dorzolamide–timolol were for the generic version of the drug.[22]

Combination therapies: dorzolamide–timolol and brinzolamide–brimonidine

Combination agents such as dorzolamide–timolol (Cosopt, FDA approved 1998) and brinzolamide–brimonidine (Simbrinza, FDA approved 2013) have been widely used in lowering IOP and improving compliance (table 1).[12] In patients initially taking four separate medications, switching to latanoprost–timolol and brinzolamide–brimonidine significantly improved IOP and compliance outcomes.[12] Another study showed that brinzolamide–brimonidine added to a prostaglandin analogue had superior IOP lowering ability than a prostaglandin analogue alone.[63] Brinzolamide–brimonidine and dorzolamide–timolol combination therapy in a single drop were both shown to be non-inferior to each of the component agents administered individually. Additionally, their increased convenience may be beneficial to individuals that require multiple eye drops or those that cannot tolerate beta-blocking agents.[64 65] The same was true for dorzolamide–timolol.[52–56 58–68] These combination therapies were also shown to be effective and safe for lowering IOP in normal-tension glaucoma patients.[69] Brinzolamide–brimonidine combination drops added to a prostaglandin analogue was also shown to improve mean diurnal IOP greater than prostaglandins alone.[70] CAIs may be used when second-line beta blockers are contraindicated, although they are often more effective in combination with a beta-blocker.[71]

Topical CAI impact on ocular haemodynamics

OAG has been associated with blood flow abnormalities for many decades with decreased ocular perfusion in multiple tissue beds being linked to structural and functional glaucoma progression.[15] While the vasodilatory effects of the systemic CAI acetazolamide are well established, the question as to whether topical CAIs can similarly increase choroidal and retinal blood flow has been a topic of great interest in the past two decades. Dorzolamide has been demonstrated to relax pericytes in one study, suggesting a mechanism for increasing flow in the small vessels of the eye.[72] Dorzolamide has also been found to increase fundus pulsation.[73] The same effect has been seen in response to acetazolamide with increased fundus pulsation owing to a decrease in the resistive index of the ophthalmic artery.[74] Similarly, decreased vascular resistance in the ophthalmic artery has been observed in response to dorzolamide.[75] Several studies outlining these effects are shown in table 2.[7 76–84] A meta-analysis published in 2009 found significantly increased peak systolic and end diastolic blood flow velocity following topical CAI therapy in the central retinal and short posterior ciliary arteries with a concomitant decreased resistive index; these findings were not seen in the ophthalmic artery.[7] The same meta-analysis found both dorzolamide and brinzolamide increased retrobulbar blood flow velocity by colour Doppler imaging. Similar results have also been observed for the combination therapies dorzolamide–timolol and brinzolamide–brimonidine.[85 86] By Poiseuille's law, vascular dilation is the only mechanism to reduce resistance in a blood vessel to affect an increase in flow velocity. Therefore, the increase in blood flow velocity observed following CAI treatment is likely secondary to direct vascular dilation.

Little comparative data on topical CAIs and ocular blood flow is available. In one study the fixed combination of dorzolamide-timolol was compared with latanoprost-timolol; only dorzolamide-timolol increased retrobulbar blood flow velocities despite both treatments demonstrating a statistically similar IOP reduction, indicating the unique role of CAIs in altering ocular blood flow.[87] Multiple other studies have demonstrated similar effects.[85 88 89]

New formulations

Several novel formulations for CAIs are currently under the investigation. For example, bifunctional CAI compounds with a nitric oxide-releasing moiety have been proposed to increase the ocular hypotensive effect of traditional CAIs via nitric oxide induced vascular relaxation.[90] This mechanistic add-on effect was observed in rabbits and monkeys where adding a NO-moiety to dorzolamide significantly increased its IOP-lowering capacity.[91 92] Additionally, other hybrid drugs including incorporating sulfonamide and prostaglandin moieties in the same molecule are under the investigation, however, current data are limited to in vitro studies.[46 93 94]

CONCLUSIONS

As newer, more efficacious chemical ocular hypotensive agents have been developed, CAIs have largely been relegated to second-or third-line agents in the management of OAG. Currently, use of CAIs may be indicated in cost-prohibitive cases or when prostaglandin analogues and/or beta-blockers are contraindicated. CAIs are rarely used as monotherapy,

and are instead usually part of combination therapies including prostaglandin analogues or beta-blockers to further reduce IOP. Topical CAIs have also been widely demonstrated to be capable of increasing biomarkers of ocular blood flow via chemically mediated vasodilatory mechanisms, although their exact relevance to OAG onset and progression remains unconfirmed.[7] More recent topical formulations of CAIs using nitric oxide moieties[95] or novel delivery methods[71 95 96] are under the investigation and may lead to a greater usage of CAIs by clinicians in the near future.[90] There is also ongoing research into pairing existing CAIs with chemical structural moieties such as sulfonylureas and sulfonylthioureas to increase the specificity of binding to carbonic anhydrase isoforms[93] that may lead to an increase in use of CAIs for future glaucoma management.

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Table 1

Effect of topical carbonic anhydrase inhibitors on intraocular pressure and visual function

Agent	Author	Study type	Subjects (total n)	IOP reduction	Time captured	Visual field changes
Brinzolamide	Siesky[7]	Meta-analysis	OAG (15)	No change	3 months	No change
Brinzolamide	Silver[44]	RCT	OAG, OHT (148)	−5.0	3 months	No change
Brinzolamide	Li[24]	Meta-analysis	2 studies (NR)	−2.2	N/A	No change
Brinzolamide	Aung[97]*	RCT	OAG, OHT (178)	−7	6 months	NR
Brinzolamide additive to PG or beta blocker	Liu[98]*	Meta-analysis	OAG or OHT (312(5 studies))	−3.8	24 hours to 5 years (mean=14.4 months)	NR
Brinzolamide/brimonidine	Aung[97]*	RCT	OAG, OHT (160)	−7.7	6 months	NR
Brinzolamide/brimonidine additive therapy	Moosavi[12]	Retrospective	OAG or OHT (76)	−2.8	2–17.5 months (mean=5.4 months)	NR
Dorzolamide	Bernd[57]	Retrospective	OAG (28)	−2.5	9 months	VF improved significantly by 18%
Dorzolamide	Siesky[7]	Meta-analysis	OAG (15)	No change	3 months	No change
Dorzolamide	Silver[44]	RCT	OAG, OHT (149)	−4.8	3 months	No change
Dorzolamide	Li[24]	Meta-analysis	4 studies (NR)	−1.9	N/A	No change
Dorzolamide	Boyle[66]*	RCT	OAG or OHT (109)	−4.6	3 months	NR
Dorzolamide additive to PG or beta blocker	Liu[98]*	Meta-analysis	OAG or OHT (316 (5 studies))	−3.6	N/A	NR
DTFC	Kim[67]	Retrospective	tx-naïve OAG (37)	−3.7	12 weeks	NR
DTFC	Boyle[66]*	RCT	OAG or OHT (114)	−7.7	3 months	NR

*Used first morning value when multiple were available.

DTFC, dorzolamide/timolol fixed combination; N/A, not applicable; NR, not recorded; OAG, open angle glaucoma; OHT, ocular hypertension; PG, prostaglandin analogues; RCT, randomised controlled trial; VF, visual field.

Table 2

Blood flow outcomes of carbonic anhydrase inhibitors

Drug	Author	Findings
DTFC	Moss[76]	Increased pulse volume by 0.767 μL (p=0.0087) compared with latanoprost Increased ocular pulse amplitude during pulsatile ocular blood flow compared with timolol alone DTFC associated with an increased retrobulbar flow velocity measured with colour Doppler imaging DTFC increased end diastolic velocity (p=0.0168), and decreased resistance to flow (p=0.0279) in the central retinal artery
DTFC	Manni[77]	Significantly increased pulsatile ocular blood flow compared with timolol alone (p=0.0079)
DTFC	Traustason[78]	Significant decrease in arteriolar (p<0.01) and venular saturation (p<0.5) when switched from DTFC to timolol alone
DTFC, BTFC	Martínez[79]	DTFC significantly increased end diastolic velocity in the ophthalmic artery (p<0.001) DTFC significantly reduced the resistivity index in the ophthalmic artery (p<0.001) DTFC significantly reduced the resistivity index in the ophthalmic artery, central retinal artery and short posterior arteries (p<0.001) No significant effects were not seen in the BTFC group
DTFC	Siesky[80]	DTFC reduced the no of zero blood flow pixels in the superior (p<0.014) and inferior (p<0.008) retina in non-glaucomatous groups DTFC also reduced the numbers of zero blood flow pixels in the inferior retina (p<0.006) in the glaucomatous group
DTFC, BTFC	Martínez[81]	Visual field progression risk was lower in DTFC therapy (HR=0.65, 95% CI 0.41 to 0.90) compared with BTFC therapy
Dorzolamide	Mayama[82]	Increase in optic nerve head blood flow by 5%–15% detected by Heidelberg retinal flowmeter
Dorzolamide	Huber-van der Velden[83]	Dorzolamide application prior to oculopression was shown to significantly increase peak systolic velocity in the ophthalmic artery compared with oculopression alone (14%; p<0.0001) End-diastolic velocity in the short posterior ciliary arteries was significantly higher in the dorzolamide/oculopression group (21%; p<0.0001) The resistivity index of the short posterior ciliary arteries was significantly lower in the dorzolamide/oculopression group (−5.6%; p=0.001)
Dorzolamide	Venkataraman[84]	After treatment with topical 2% dorzolamide for 2 weeks the treated OAG group showed a significant increase in diameter, velocity and flow (p<0.04) in response to normoxic hypercapnia
Dorzolamide	Siesky[7]	Increased blood flow (p<0.001)
Brinzolamide	Siesky[7]	Increased blood flow (p<0.001)

BTFC, brinzolamide/timolol fixed combination; DTFC, dorzolamide-timolol fixed combination; OAG, open angle glaucoma.