ECRONICON OPEN ACCESS

EC OPHTHALMOLOGY
Mini Review

Rediscovering Carbonic Anhydrase Inhibitors in Ophthalmology

Marianne L. Shahsuvaryan*

Professor of Ophthalmology, Yerevan State Medical University, Republic of Armenia

***Corresponding Author**: Marianne L. Shahsuvaryan, Professor of Ophthalmology, Yerevan State Medical University, Republic of Armenia.

Received: December 03, 2016; **Published:** December 14, 2016

Abstract

Background: Topical carbonic anhydrase inhibitors (CAI) are the commonly used pharmacologic agents as an ocular hypotensive in medical therapy of glaucoma. This traditional use is due to reduced aqueous production through decreased bicarbonate formation in ciliary body epithelium. Taken into account current economical burden worldwide, the well-known drugs are "rediscovered' and repurposed. In this light of view CAI are highlighting new properties and new targets in modern ophthalmology.

Objective: The objective of this review is to evaluate the evidence and discuss the rationale behind the recent suggestions that carbonic anhydrase inhibitors may be useful in therapy of retinitis pigmentosa.

Keywords: *Carbonic Anhydrase Inhibitors; Dorzolamide; Antiedematic Effect; Macular Edema; Retinitis Pigmentosa*

Introduction

Carbonic anhydrase inhibitors (CAI) are sulfonamide derivatives. The main drug from this group is Acetazolamide. Acetazolamide is a diuretic acting by inhibition of enzyme carbonic anhydrase, responsible for H^+ ions transport in the human organism, resulting to metabolic acidosis due to increased renal elimination of Na/HCO_3 and K^+, and decreased plasma bicarbonate respectively [1]. In ophthalmology Acetazolamide is used to rapid decrease of IOP in angle-closure glaucoma attack, in secondary glaucoma and as an additional supplementary therapy in primary open-angle glaucoma [2].

Latter topical CAI- Dorzolamide and Brinzolamide were introduced. One of the major reasons for their use in the topical nature of administration results in the lowered systemic side effects seen with oral Acetazolamide use such as drowsiness, confusion, allergic reactions, paraesthesias, myelosuppression, renal calculi, loss of potassium, or hyperchloremic metabolic acidosis from extended use, and became the commonly used pharmacologic agents as an ocular hypotensive in medical therapy of glaucoma. Traditionally, due to the ability to reduce aqueous production through decreased bicarbonate formation in ciliary body epithelium. Besides in contrast to acetazolamide, dorzolamide has a lipid soluble nature and high affinity for carbonic anhydrase, which significantly increases a bioavailability of the drug [3].

In the past few years there has been an increased interest in drug reprofiling due to sustained high failure rates and the rising costs involved in attempts to bring new drugs to the market [4].

Currently repurposing or "rediscovering" of approved drugs is widely accepted by the industry and encouraged by worldwide regulatory agencies. The general use of an approved medication for a new indication recognized by the medical community but not specifically indicated by a regulatory agency (FDA) is referred to as off-label use. Once the FDA approves a drug, ophthalmologists may prescribe the drug for an unapproved use when they judge that it is medically appropriate for their patient. Specifically, the exploration of CAI use in retinitis pigmentosa (RP) was a result due to a lack of treatment in effect. As researchers and practitioners considered the properties of CAI, it became reasonable to trial them in RP patients with macular edema.

The goal of this review is to highlight new properties of carbonic anhydrase inhibitors and their clinical implications in modern ophthalmology as an off-label use.

Currently discovered properties of CAI

Carbonic anhydrase, as an one of the most ubiquitous enzyme systems in the body, acting also an inflammatory mediator, besides ciliary body epithelium is also found in the red-green cones, within the Mueller cells of the retina, and in the retinal pigment epithelium (RPE), thus revealing new intraocular targets. The new action mechanisms of CAI are discovered. CAI have been shown to have direct effects both on retinal and retinal pigment epithelial cell function by inducing an acidification of the subretinal space, a decrease of the standing potential as well as an increase in retinal adhesiveness. It is thought that acidification of the subretinal space is finally responsible for the increase in fluid resorption from the retina through the RPE into the choroid [5].

Pump function of dorzolamide has been confirmed in multiple clinical studies of patients with X-linked retinoschisis by reducing macular and midperipheral retinoschisis [6-10].

Antiedematic effect of CAI

Carbonic anhydrase plays a role in the biochemical reactions cascade in the universal pathomechanisms of cystoid macular edema (CME), where prostaglandins accelerate vascular permeability causing leakage and upregulate generation of vascular endothelial growth factor (VEGF) and carbonic anhydrase-1 (CA-1) expression and downregulation of K+ channels in Müller cells, resulted to increasing the inflow and reducing the outflow of ions and fluid from the inner nuclear layer and Henle fiber layer in the macular region [11].

Antiedematic effect of CAI is realized by increasing the fluid hydrodynamics through RPE and pump function due to acidification of the subretinal space thus controlling and adjusting the extracellular pH gradients produced by the metabolic activity of cells [5,12,13], and at the same time by suppression of the inflammatory process underlying the vascular and RPE leakage causing the CME as was shown above [11].

CAI drops alone have been known to be effective for treatment of macular edema in several ocular conditions [5]. They have been shown to reduce edema in patients with choroideremia [14] and more recently were included in a treatment regimen for Vogt–Koyanagi–Harada disease [15] and recommended for syndromic retinal dystrophies such as Alström syndrome [16], and also for CME after cataract extraction [17].

Predictably rational current use of CAI in Retinitis Pigmentosa

Retinitis pigmentosa (RP) is a genetically heterogeneous group of inherited retinal dystrophies caused by progressive loss of photoreceptors and characterized by night blindness, peripheral visual field loss, and retinal pigment deposits visible on fundus examination, affecting two million people worldwide [18].

CME is a well confirmed cause of visual loss in patients with RP, with a prevalence ranging from 10 to 40%. [19,20]. Various treatment modalities have already been attempted for the treatment of CME in RP patients, including systemic or topical CAI [7,21-25]. Study of RP patients with CME revealed a correlation between anticarbonic anhydrase antibodies and CME [26] thus advocating CAI use in this condition.

Earlier reports showed a recurrence of CME in patients with RP by oral CAI [22,27]. While a previous study by Fishman and Apushkin [23] has shown a beneficial effect from the use of a topical form of CAI in patients with RP, their study had a limited number of patients followed for a short period of time. Genead., *et al.* [7] initiated a study to determine the efficacy for sustained use of topical therapy with dorzolamide hydrochloride 2% on visual acuity and cystic macular lesions verified by OCT, in 32 patients with retinitis pigmentosa and Usher syndrome over a more extended period of time. The authors evidenced that treatment of CME in afore mentioned patients with topical dorzolamide can reduce central foveal thickness in a notable percentage of cases with improvement of visual acuity in some cases.

Similar results were obtained by Ikeda Y [25] in more recent study. The authors enthusiastically concluded on the long-term efficacy - durated longer than 1 year of topical dorzolamide in CME.

In conclusion, based on currently available findings CAI, specifically Dorzolamide can be effective for CME therapy in retinitis pigmentosa in daily clinical practice and should be considered as a viable treatment option. Following the statement " Everything new is well forgotten old", carbonic anhydrase inhibitors were rediscovered enriching by new properties and new avenue of ocular pharmacotherapy being explored.

Bibliography

1. Kaplan NM. "Diuretics as a basis of antihypertensive therapy. An overview". *Drugs* 59.2 (2000): 21-25; discussion 39-40.

2. Kaur IP., *et al*. "Review Acetazolamide: future perspective in topical glaucoma therapeutics". *International Journal of Pharmaceutics* 248.1-2 (2002): 1-14.

3. Kellner U., *et al*. "[Hereditary retinochoroidal dystrophies. Part 2: differential diagnosis]. *Ophthalmologe* 101.4 (2004): 397-414.

4. Tobinick EL. "The value of drug repositioning in the current pharmaceutical market". *Drug News and Perspectives* 22.2 (2009): 119-125.

5. Wolfensberger TJ. "The role of carbonic anhydrase inhibitors in the management of macular edema". *Documenta Ophthalmologica* 97.3-4 (1999): 387-397.

6. Collison FT., *et al*. "Resolution of mid-peripheral schisis in X-linked retinoschisis with the use of dorzolamide". *Ophthalmic Genetics* 35.2 (2014): 125-127.

7. Genead MA., *et al*. "Efficacy of sustained topical dorzolamide therapy for cystic macular lesions in patients with X-linked retinoschisis". *Archives of Ophthalmology* 128.2 (2010): 190-197.

8. Thobani A and Fishman GA. "The use of carbonic anhydrase inhibitors in the retreatment of cystic macular lesions in retinitis pigmentosa and X-linked retinoschisis". *Retina* 31.2 (2011): 312-315.

9. Ali S and Seth R. "X-linked juvenile retinoschisis in females and response to carbonic anhydrase inhibitors: case report and review of the literature". *Seminars in Ophthalmology* 28.1 (2013): 50-54.

10. Sadaka A and Sisk RA. "Dramatic regression of macular and peripheral retinoschisis with dorzolamide 2 % in X-linked retinoschisis: a case report". *Journal of Medical Case Reports* 10 (2016): 142.

11. Bringmann A., *et al*. "Pathomechanisms of cystoid macular edema". *Ophthalmic Research* 36.5 (2004): 241-249.

12. Cox SN., *et al*. "Treatment of chronic macular edema with acetazolamide". *Archives of Ophthalmology* 106.9 (1988): 1190-1195.

13. Gallemore RP., *et al*. "Retinal pigment epithelial transport mechanisms and their contributions to the electroretinogram". *Progress in Retinal and Eye Research* 16.4 (1997): 509-566.

14. Genead MA., *et al*. "Topical dorzolamide for treatment of cystoid macular edema in patients with choroideremia". *Retina* 32.4 (2012): 826-833.

15. Onishi SM., *et al*. "Topical difluprednate for the treatment of Harada's disease". *Clinical Ophthalmology* 9 (2015): 157-167.

16. Larrañaga-Fragoso P., *et al*. "Topical carbonic anhydrase inhibitors in macular edema associated with Alström syndrome". *Ophthalmic Genetics* 37.4 (2016): 427-429.

17. Asahi MG., *et al*. "Strong topical steroid, NSAID, and carbonic anhydrase inhibitor cocktail for treatment of cystoid macular edema". *International Medical Case Reports Journal* 8 (2015): 305-312.

18. Busskamp V., *et al*. "Optogenetic therapy for retinitis pigmentosa". *Gene Therapy* 19.2 (2012): 169-175.

19. Hajali M., *et al*. "The prevalence of cystoid macular oedema in retinitis pigmentosa patients determined by optical coherence tomography". *British Journal of Ophthalmology* 92.8 (2008): 1065-1068.

20. Hajali M and Fishman GA. "The prevalence of cystoid macular edema on optical coherence tomography in retinitis pigmentosa patients without cystic changes on fundus examination". *Eye* 23.4 (2009): 915-919.

21. Fishman GA., *et al*. "Acetazolamide for treatment of chronic macular edema in retinitis pigmentosa". *Archives of Ophthalmology* 107.10 (1989): 1445-1452.

22. Apushkin MA., *et al*. "Rebound of cystoid macular edema with continued use of acetazolamide in patients with retinitis pigmentosa". *Retina* 27.8 (2007): 1112-1128.

23. Fishman GA and Apushkin MA. "Continued use of dorzolamide for the treatment of cystoid macular edema in patients with retinitis pigmentosa". *British Journal of Ophthalmology* 91.6 (2007): 743-745.

24. Ikeda Y., *et al*. "The clinical efficacy of a topical dorzolamide in the management of cystoid macular edema in patients with retinitis pigmentosa". *Graefe's Archive for Clinical and Experimental Ophthalmology* 250.6 (2012): 809-814.

25. Ikeda Y., *et al*. "Therapeutic effect of prolonged treatment with topical dorzolamide for cystoid macular oedema in patients with retinitis pigmentosa". *British Journal of Ophthalmology* 97.9 (2013): 1187-1191.

26. Wolfensberger TJ., *et al*. "Antiretinale Antikörper assoziiert mit zystoidem Makulaödem". *Klinische Monatsblätter für Augenheilkunde* 216.5 (2000): 283-285.

27. Fishman GA., *et al*. "Rebound of macular edema with continued use of methazolamide in patients with retinitis pigmentosa". *Archives of Ophthalmology* 111.12 (1993): 1640-1646.

Volume 4 Issue 4 December 2016