ORIGINAL ARTICLE

Effects of Topical Dorzolamide on Serum Potassium Levels

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Abstract:

Objective: To evaluate how serum potassium levels are affected by a 2% ocular solution of dorzolamide.

Methods: This study was conducted at the Department of Ophthalmology, Lahore General Hospital, Lahore. A total of 55 patients, with diagnosed cases of primary open-angle glaucoma were enrolled. All participants were prescribed dorzolamide 2% eye drops twice daily in both eyes. Serum potassium levels were recorded at baseline and then monitored monthly for four months. Data was analyzed by using SPSS version 22, and paired sample *t*-tests were applied to compare potassium levels at 2nd, 3rd and 4th month.

Results: Of the 55 patients, 28 (50.9%) were male and 27 (49.1%) were female, with a mean age of 49 years. The mean baseline serum potassium level was 3.94 ± 0.31 mEq/L. A significant reduction was observed in serum potassium levels from baseline to all follow-up visits, as assessed by paired sample t-test. At 1 month, the mean reduction was 0.21 mmol/L ($p < 0.001$), which increased to 0.46 mmol/L at 2 months ($p < 0.001$). By 3 months, the decline reached 1.03 mmol/L ($p < 0.001$), and at 4 months, the maximum reduction of 1.47 mmol/L was noted ($p < 0.001$).

Conclusion: Topical dorzolamide 2% is associated with a significant and progressive decline in serum potassium levels with continued use. Regular monitoring of electrolyte levels may be advisable in patients on long-term dorzolamide therapy to prevent potential complications of hypokalemia. *Al-Shifa Journal of Ophthalmology 2025; 21(3): 192-197.*

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Originally Received: 05 March 2025
Revised:13 April 2025
Accepted: 3 June 2025

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Introduction:

Glaucoma, which quietly takes away vision, is treated with a type of eye medicine called carbonic anhydrase inhibitors (CAIs)[1]. These include both eye drops, like dorzolamide hydrochloride 2% solution and brinzolamide 1% suspension, and oral medications, such as methazolamide, acetazolamide, and dichlorphenamide[1]. These medicines work by lowering the pressure inside the eye. They do this by reducing the amount of fluid, called aqueous humor, that the eye makes[2]. Normally, water from the non-pigmented ciliary body combines with carbon dioxide to form carbonic acid, which then splits into protons and bicarbonate ions.

This process is helped by an enzyme called carbonic anhydrase, specifically isoenzyme II and possibly IV[3]. This water then moves into the back part of the eye, creating an osmotic gradient. This gradient helps move water from the ciliary stromal vessels, forming the aqueous humor[1, 4].

Carbonic anhydrase inhibitors stop this enzyme from working, reducing the production of bicarbonate ions. This lowers the osmotic gradient, which in turn reduces the amount of aqueous humor made, lowering the eye pressure[1].

Besides the eye, carbonic anhydrase is also found in the kidneys, red blood cells, and respiratory system[5]. In the kidneys, this enzyme helps reabsorb sodium, potassium, and bicarbonate and also helps get rid of protons and carbonic acid[6]. When CAIs block the enzyme in the kidneys, it leads to increased urine production, called diuresis[4]. Because carbonic anhydrase is widespread in the body, taking oral CAIs can cause different side effects, such as metabolic acidosis, low potassium (hypokalemia), high chloride levels (hyperchloremia), and stomach issues like loss of appetite, vomiting, and diarrhea [7,8,9].

Topical CAIs are better than oral ones because they cause fewer side effects while still being effective[8]. Even though a large amount of the drug from dorzolamide eye drops goes into the bloodstream, most of the noticeable side effects are reduced. The two most common side effects of using dorzolamide eye drops are a short-lived bitter taste and a burning feeling in the eyes[6]. The study drug, dorzolamide 2%, is available at a low cost in the local market, making it affordable for people with lower incomes Hypokalemia is a known side effect of oral carbonic anhydrase inhibitors, but there is not much information on whether topical ones, like dorzolamide, can also cause low potassium levels.

This study aims to look at how 2% dorzolamide eye drops affect the body's metabolism by checking the levels of potassium in the blood.

Methodology:

This quasi-experimental before–after study was conducted in the Department of Ophthalmology, Lahore General Hospital, Lahore, between July 1, 2024, and November 15, 2024. Ethical approval for this study was obtained from the Institutional Review Board of Lahore General Hospital.

The sample size of 55 was determined using a 95% confidence level, 80% power of the study, and estimates from previous literature. A non-probability consecutive sampling method was employed for patient selection.

Patients aged between 35 to 65 with a confirmed diagnosis of primary open-angle glaucoma and who were prescribed dorzolamide 2% ophthalmic solution at the standard dosage of two drops per day in both eyes were included. Exclusion criteria consisted of patients already receiving other antiglaucoma medications, and those with a prior history of ocular surgery, or those suffering from systemic illnesses that could affect serum potassium levels.

At baseline, each participant underwent a complete ophthalmic and systemic assessment. Serum potassium levels were recorded before starting treatment and subsequently monitored at monthly intervals for four months. Data was collected and entered in SPSS 22 for analysis.

Descriptive statistics were used for demographic and clinical variables, and a paired sample t-test was applied to compare serum potassium levels before and after treatment.

Results:

A total of 55 patients were included in the study, comprising 28 males (50.9%) and 27 females (49.1%), with a mean age of 49 years (Table 1).

Table 1: Distribution of patients according to gender

Gender	No. of patients	Percentage
Males	28	50.91%
Females	27	49.09%
Total	55	100%

Table 2: Paired Samples Test of Serum Potassium Levels at Different Follow-Up Periods

Pair	Comparison (Serum Potassium)	Mean Difference (mmol/L)	Std. Deviation	Std. Error Mean	95% CI of Difference (Lower)	95% CI of Difference (Upper)	t-value	df	p-value
1	Baseline – 1 month	0.214	0.274	0.037	0.141	0.289	5.811	54	<0.001
2	Baseline – 2 months	0.458	0.302	0.041	0.376	0.540	11.242	54	<0.001
3	Baseline – 3 months	1.029	0.438	0.059	0.911	1.147	17.430	54	<0.001
4	Baseline – 4 months	1.465	0.403	0.054	1.356	1.574	26.946	54	<0.001

A significant reduction was observed in Serum potassium levels from baseline to all follow-up visits, as assessed by paired sample t-test. At 1 month, the mean reduction was 0.21 mmol/L ($p < 0.001$), which increased to 0.46 mmol/L at 2 months ($p < 0.001$). By 3 months, the decline reached 1.03 mmol/L ($p < 0.001$), and at 4 months, the maximum reduction of 1.47 mmol/L was noted ($p < 0.001$).

Discussion:

Most topical drugs are believed to enter the eye through the cornea. However, the front part of the eye, called the anterior chamber, can also be reached through the limbus or sclera. Before being found in the fluid inside the eye (aqueous humor), dorzolamide has been shown to collect in the ciliary body. This means it can enter the eye from areas other than the cornea. Researchers found that dorzolamide can pass through the cornea more quickly than acetazolamide, suggesting that it may also enter the eye through the limbus and/or sclera. After applying the drug to both eyes, about 80% of it is absorbed into the body through the conjunctiva or the mucous membranes in the nose and throat, then drains out through the nasolacrimal duct[6,10]. Red blood cells quickly absorb carbonic anhydrase inhibitors (CAIs) once they are in the bloodstream. Carbonic anhydrase isoenzymes I and II are found in red blood cells. When dorzolamide enters the bloodstream, it is broken down into a substance called N-deethyl-dorzolamide, as found in a high-performance liquid chromatography test[11]. This breakdown product has a stronger tendency to bind with carbonic anhydrase I, whereas the original form (dorzolamide) has a stronger affinity for carbonic anhydrase II[12]. After using dorzolamide for four weeks, the activity of carbonic anhydrase II in red blood cells drops to about 21% of the original level[13]. Interestingly, this low level doesn't cause noticeable side effects, but it can lead to lower levels of potassium in the blood[14]. Since dorzolamide doesn't bind tightly to plasma proteins and stays in red blood cells, it and its breakdown product leave the body slowly, possibly taking months to fully clear[14]. The kidneys are mainly responsible for removing dorzolamide and its metabolites from the body, and the overall role of metabolism in this process is minor.

Topical CAIs reduce eye pressure by decreasing the production of aqueous humor. In both humans and monkeys, studies using fluorophotometry have shown that this pressure-lowering effect occurs because inhibiting carbonic anhydrase in the ciliary body reduces the production of bicarbonate, one of the key steps in forming aqueous humor. There are seven known types of carbonic anhydrase isoenzymes, labeled from I to VII. In humans, there are at least four different types. These isoenzymes have different activities, binding properties, and can be stained with specific antibodies. Dorzolamide is much more effective against carbonic anhydrase type II than against types IV or I, being

approximately 38 times more effective against type IV and around 1,000 times more effective against type I. Different organs contain these isoenzymes in different amounts, and even within a single cell, multiple types may be present. Initially, it was thought that the effect of CAIs on isoenzyme II caused the reduction in aqueous humor production. However, carbonic anhydrase II is abundant in the ciliary body, and in patients who lack this isoenzyme, acetazolamide doesn't lower intraocular pressure[15].

Using topical antiglaucoma treatments, like carbonic anhydrase inhibitors, can lead to several side effects, including watering and blurry vision (9%), a burning or foreign body sensation (12%), and stinging (7%). These effects are more common with CAIs compared to other medications like timolol 0.5% or betaxolol 0.5%[16]. The low pH at which dorzolamide is stored causes these burning and stinging feelings, which can lead to the drug being washed out. A bitter or metallic taste is one of the most common side effects of dorzolamide, occurring in about 27% of people. This may be due to bicarbonate accumulation and reduced carbonic anhydrase activity in taste buds caused by the drug entering the mouth through the tear ducts.

Systemic side effects from using topical CAIs are not often reported[17, 18]. Previous studies suggest that systemic adverse effects are minimized when dorzolamide levels in the blood only slightly inhibit CA isoenzymes outside the ciliary body[3, 6, 19]. Systemic CAIs can cause metabolic acidosis, electrolyte imbalances, and the formation of kidney stones. According to Martens and Banditt, topical CAI use can also lead to metabolic acidosis and hypokalemia, which are the most frequent side effects of systemic CAI therapy. The kidneys slowly remove dorzolamide and its breakdown products over a period of about four months, and they are excreted in the urine[6, 20, 20], and Prolonged use of dorzolamide can lead to systemic accumulation[17]. Differential diagnoses for a patient's metabolic acidosis and hypokalemia include gastrointestinal losses, primary kidney disease, renal tubular acidosis (RTA), and fluid diuresis. Without a history of vomiting or diarrhea, excessive potassium loss through non-renal pathways is unlikely, and primary kidney disease was ruled out based on normal urine concentrating ability. Therefore, the most likely cause of hypokalemia is the systemic absorption and slow buildup of dorzolamide and its metabolites.

A double-blind, randomized, placebo-controlled study in 12 healthy volunteers was conducted to assess the systemic effects of 3% dorzolamide[21]. All participants followed a controlled diet for five days before and during the study. They used 3% dorzolamide four times a day in both eyes for two weeks. Blood and urine levels of electrolytes and acid-base balance were checked one day before starting the treatment and on days 1, 7, and 14, and 24-hour urine samples were collected daily. No significant changes were observed in these measurements compared to pre-treatment levels. In a study of 27 cats, eight (29.6%) showed signs of metabolic acidosis with normal serum electrolytes after being given topical 2% dorzolamide. No significant changes in sodium, chloride, glucose, ALT, or ALP were seen in any of the cats[22]. In contrast to potassium, no significant changes from baseline were found for sodium (P = .0798), chloride (P = .5569), glucose (P = .5758), ALT (P = .0738), or ALP (P = 1.0000) in any of the cats.

A five-day-old infant with bilateral Peter's anomaly was given topical dorzolamide three times a day.On the seventh day of treatment, the infant showed signs of metabolic acidosis with normal serum electrolytes. The symptoms improved when the medication was stopped[23]. A cohort study[24] concluded that patients with primary open-angle glaucoma and advanced chronic kidney disease are at increased risk of developing metabolic acidosis when using topical carbonic anhydrase inhibitors. Therefore, elderly

patients, infants, and those with kidney issues should be closely monitored for any adverse effects caused by reduced elimination. As far as we know, this is the first study in our local population looking at how bilateral topical dorzolamide affects things. But there are some important limitations. One is that we didn't include information about the patient's background and behavior. Another is that we didn't check the blood levels of CAI after giving the medication. Additionally, using the drug on both eyes may increase the amount of medicine in the body compared to using it on just one eye, which could help explain the drop in blood potassium levels. We suggest future research with more participants, longer observation periods, and regular checks of blood chemistry to better understand these effects.

Conclusion:

The study has concluded a decline in the serum potassium levels after the administration of 2% dorzolamide eye drops. Serum potassium level monitoring is also advised in patients on long term bilateral dorzolamide therapy. Our study highlights the novel findings of potassium decline with bilateral dorzolamide use in the local population, emphasizing the importance of biochemical monitoring.

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