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Revisiting acidosis in acetazolamide treatment of severe glaucoma: A case report

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1. Introduction

Carbonic anhydrase inhibitors are commonly used systemic medications that lower intraocular pressure (IOP) in glaucoma. These drugs have numerous ophthalmic indications including primary open-angle glaucoma, secondary glaucoma, and preoperatively in acute angle-closure glaucoma where delay of surgery is required.[1] Among the oral medications in this class, acetazolamide is often the drug of choice in the management and treatment of glaucoma. It acts on carbonic anhydrase II (CA II), thereby affecting bicarbonate transport into the posterior chamber of the eye and reducing aqueous humor.[2–4] The effect of acetazolamide on CA II is an order of magnitude greater than that of non-sulfonamide CA inhibitors.[5]

Outside of the eye, acetazolamide blocks the reabsorption of bicarbonate at the proximal tubule in the kidney leading to alkalinization of the urine. The drug has been used to counteract metabolic alkalosis.[6] Acetazolamide also blocks the conversion of bicarbonate to CO2 in pulmonary capillaries causing an accumulation of CO2. In healthy patients this causes an increased minute ventilation and ventilatory drive. However, in patients with severe COPD, decreased ability for respiratory compensation in the face of metabolic acidosis may lead to prolonged and severe metabolic acidosis.[7,8]

Here we present an unusual and highly instructive case where a patient with COPD experienced severe metabolic acidosis as a result of acetazolamide use prescribed for glaucoma.

2. Case report

A 73-year-old man with a 10-year history of open angle glaucoma, diabetes mellitus type 2, 148 pack-year history of cigarette smoking, and COPD presented to the Emergency Department (ED) with a headache. He had been previously diagnosed with glaucoma, which was refractory to medical management, and was referred to a regional ocular surgeon after he had demonstrated non-improvement and continued to endorse vision loss while on maximal medical therapy, with a regimen of latanoprost QHS OU, dorzolamide-timolol BID OU, brimonidine TID OU, PreserVision BID PO, and acetazolamide 500mg BID PO.

The patient had surgery in the right eye with intraocular lens implant for cataract as well as Baerveldt 250 glaucoma drainage implant with corneal patch graft for medically uncontrolled glaucoma 8 days prior to ED presentation. He previously had similar surgery of the left eye one month prior, again with Baerveldt 250 implant with corneal patch graft and intraocular lens implant for cataract. Following the right eye procedure, the patient discontinued taking acetazolamide 500 mg BID which he had been prescribed for approximately 7 months. While in the ED he underwent fluorescein examination with no corneal uptake. His left eye tonometry measurement was 22, however, the Tono-Pen was unable to recalibrate to measure his right eye. He had routine labs drawn during ED encounter (Table 1: “6 weeks prior”, with bicarbonate value of 25 and anion gap of 11 on chemistry, but there was no venous blood gas performed during the encounter. He was given Toradol and Tylenol which improved his headache. The ocular surgeon was consulted and the patient was discharged to follow up with his general ophthalmologist as recommended.

Approximately 6 weeks later the patient was seen by his ocular surgeon. At the time his IOP was 16 and 29 mm Hg OD and OS, respectively. He was re-initiated on acetazolamide 500 mg BID at the time of the clinic visit. The patient returned to the ED 2 weeks later with complaints of vomiting, confusion, rash, and mild headache. He reported normal bowel movements and denied any diarrhea or abdominal pain. His labs revealed a severe metabolic acidosis with a VBG pH of 7.19, HCO3 of 12 mmol/L, and pCO2 of 33 mmHg (Table 1: “1st

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presentation"). His creatinine was measured to be 1.3 mg/dL, with prior baseline value of 1.0 mg/dL, and his GFR was calculated to be 54 (prior value of 74). A chest x-ray showed bilateral chronic lung infiltrates and CT of the abdomen and pelvis with contrast was significant for nonspecific gastroenteritis without other acute pathology. He was given IV fluids and admitted to the hospital. The patient was discharged from the hospital 3 days later with a diagnosis of gastroenteritis, metabolic acidosis, dehydration, and acute kidney injury. At this time, the cause of the acidosis was believed to be from gastrointestinal losses and vomiting, though the patient did not report diarrhea at this time. The contribution of acute renal insufficiency was not discussed in documentation, and there was no discussion of acetazolamide in documentation.

The patient was seen for intraocular pressure (IOP) follow up at his ophthalmologist 2 weeks following his hospital admission. At this time his pressures were 8 and 9 in OD and OS and he was instructed to continue his acetazolamide regimen as prescribed. He was seen in the ED again 3 weeks later for 4 days of post-tussive emesis. At this time, he had a self-reported 24-pound weight loss over 2 months. He stated he had increased sputum production and had not had a bowel movement in 4 days. He denied having diarrhea. The patient had severe metabolic and respiratory acidosis with a pH of 7.19, pCO2 of 43 mmHg, and HCO3 of 16 (Table 1: 2nd presentation") on venous blood gas. His GFR was similar to previous at 59, with creatinine of 1.2. During this visit, it was discovered the patient was taking the acetazolamide which was not in his reconciled medications during his previous visits. After discussion with ophthalmology, in light of uncontrolled ongoing high ocular pressures, the patient was instructed to continue the therapy and sodium bicarbonate was prescribed to assist with acidosis thought related to this medication until follow up with ophthalmology. He was scheduled for further management of his glaucoma with his local ophthalmologist, who then discontinued acetazolamide after recheck of ocular pressures (8 OD and 10 OS). The patient was also scheduled to follow up with a pulmonologist for the first time.

The patient presented again to the ED for a COPD exacerbation 4 weeks later. A chest CT showed severe upper lobe predominant bullous emphysema and asymmetric pulmonary fibrosis, confirming the severity of his lung disease. At this time the patient was not acidotic (VBG pH = 7.46, pCO2 of 34, bicarbonate 24 on chemistry) (Table 1: "Post-acetazolamide"), strongly suggesting that his previous episodes of acidosis were due to his acetazolamide use, possibly with concomitant renal insufficiency. His GFR was 66 at this time, with creatinine of 1.1. Eventually, six months after glaucoma surgeries, pulmonary function test (PFT) demonstrated mild restrictive lung disease and severe reduction in DLCO, 39% of predicted. It was noted by the pulmonologist who performed PFT interpretation that lack of obstruction and lack of hyperinflation on PFT testing is not uncommon with severe bullous emphysema which acts as a space-occupying lesion.

3. Discussion

Acetazolamide is the most commonly used carbonic anhydrase inhibitor in the treatment of glaucoma. In addition to its action in the eye, where it acts to inhibit bicarbonate transport into the posterior chamber and thereby reduces aqueous humor, it promotes loss of bicarbonate in the urine resulting in increased acidity in the blood. In healthy individuals, this triggers a compensatory increase in respiratory rate leading to higher oxygen and lower carbon dioxide in the blood.[4] However, individuals with severe COPD, like the patient presented here, may not be able to appropriately compensate through minute ventilation.[7,8] Therefore, when prescribing acetazolamide, it is of paramount importance to consider the patient's pulmonary function. Best practice of acetazolamide use in those with chronic pulmonary disease may include screening evidence of respiratory acidosis or review of pulmonary function tests.

One must also consider the patient's age and renal function when prescribing acetazolamide since the drug is not easily metabolized and its clearance is dependent on renal function. The elderly and those with kidney disease are at risk for erythrocyte accumulation of acetazolamide, ultimately prolonging the half-life of the drug.[7,9–11] The recommended dose to treat glaucoma is 250 mg–1000 mg per day.[1] Our patient was taking the maximum daily dose. Due to his age and history of diabetes mellitus he likely had decreased renal function (creatine measured at 1.3 and 1.2 mg/dl, GFR 54–74). In his case it may have been beneficial to consider a lower dose of the medication.

This case further emphasizes the importance of a robust medication reconciliation, the process of verifying a patient's current medications. Fragmentation of medical records contributed to initial treating clinicians being unaware of our patient's full list of medications, and inappropriately attributing acidosis to gastrointestinal losses, despite lack of reported diarrhea which could cause bicarbonate losses. Further diagnostic testing could have included urine anion gap in this case, which could have suggested either high or low urinary excretion of ammonium and could have refuted diarrhea as a cause of acidosis in this patient, though the patient never demonstrated hyperchloremia (Table 1). In our patient, his prescribed acetazolamide use and the basis for his ailment remained unknown until his second presentation of metabolic acidosis. In the U.S., the incidence of preventable adverse drug events from medication errors in hospitalized patients is estimated to be approximately one medication error per patient per day.[12,13] These events can

Table 1
Key laboratory values at time of pre-diagnosis (6 weeks prior, 1st presentation, 2nd presentation) and post-acetalzolamide.

Measure	6 weeks prior (6/25)	1st presentation (8/22)	2nd presentation (10/8)	Post-Acetazolamide (11/6)
Sodium (mmol/L)	140	135	135	139
Potassium (mmol/L)	4.0	3.6	4.0	3.9
Chloride (mmol/L)	104	110	107	103
Carbon Dioxide (mmol/L)	25	12	15	22
Anion Gap	11.0	13.0	13.0	34.0
BUN (mg/dl)	16	25	25	18
Creatinine (mg/dl)	1.0	1.3	1.2	1.1
GFR calculation	74	54	59	66
Random Glucose (mg/dl)	142	172	195	131
Lactic Acid		1.8		
VBG pH		7.19	7.19	7.46
VBG pCO_2 at Pat Temp (mmHg)		32.9	42.5	34.2
VBG pO_2 (mmHg)		77	39	106
VBG HCO_3 (mmol/L)		12.3	15.7	23.5
VBG Total CO_2 (mmol/L)		13.3	17.0	24.6
VBG O_2 Saturation (%)		90.1	62.1	93.1
Carboxyhemoglobin (%THgb)		3.9	4.2	5.1
Methemoglobin (%)		0.0	0.3	0.3
Total Hemoglobin (gm/dL)		12.8	11.9	11.3

cause increased length of hospital stay, increased mortality risk, and higher costs. One technique for medical reconciliation is to include a pharmacist in the process. This has resulted in improved identification of inconsistencies in prescribed medications. One study showed that pharmacist partnership in medical reconciliation decreased adverse drug events by 43%.[14]

This case serves to heighten awareness among physicians when prescribing acetazolamide to individuals with co-morbid lung disease or renal insufficiency. Furthermore, it advocates for the importance of performing a thorough medication reconciliation.

Declaration of competing interest

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