

Acetazolamide: Considerations for Systemic Administration

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Oral acetazolamide (Diamox) is a carbonic anhydrase inhibitor that is commonly used in clinical practice as an immediate and readily available option for acute reduction of intraocular pressure (IOP). This article highlights important considerations, contraindications, and dosing adjustments for this drug to help streamline decision making in a fast-paced office setting.

Adverse Effects

The most common side effects associated with the use of oral acetazolamide include fatigue, paresthesias of the face and extremities, metallic taste in the mouth, and nausea and/or vomiting, which are related to drug-induced metabolic acidosis. Other complaints may include dizziness, weight loss, depression, or intestinal colic.

Hypokalemia. If the patient presents with several of the symptoms above, the clinician should suspect hypokalemia from urinary alkalization. It is crucial to be aware of this because hypokalemia may lead to serious morbidity from cardiac arrhythmias.

Vision changes. Patients sometimes report transient bilateral blurriness. It is caused by a bilateral myopic shift due to sulfa-related ciliary body edema and subsequent forward displacement of the iris-lens diaphragm.

Kidney stones. A serious but less common adverse effect is development of kidney stones, which occurs in 1 to 2 percent of patients.¹ The stones are

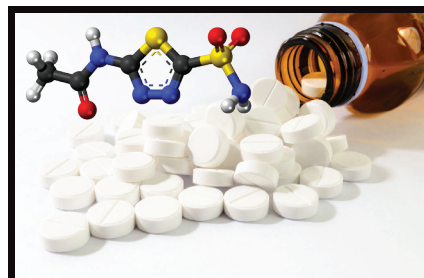
usually of the calcium phosphate or oxalate-based type due to reduced secretion of magnesium and citrate.

Taking acetazolamide and sodium bicarbonate together may increase the risk of kidney stone formation.¹ Thus, the ophthalmologist should consider the individual patient's health and medication profile when employing systemic acetazolamide.

Rare, serious complications. Rarely, acetazolamide may lead to agranulocytosis or aplastic anemia; these conditions may occur suddenly and are irreversible.¹ Therefore, if comanaged with a primary care provider, the patient should have an occasional complete blood count with differential, particularly if any worrisome signs occur, such as new-onset petechiae and fever.

Sample Case History

A 56-year-old patient with diabetes and chronic kidney disease (CKD) presents to the clinic with complaints of diminished vision and pain in the right eye. He has a history of neovascular glaucoma from proliferative diabetic retinopathy. Examination of the right eye is significant for visual acuity of 20/80; IOP of 46 mmHg despite use of topical latanoprost, timolol/dorzolamide, and brimonidine; 2+ nuclear sclerotic cataract; and a cup-to-disc ratio of 0.8. Gonioscopy reveals peripheral anterior synechiae for more than 10 clock hours. The patient has recently undergone panretinal photocoagulation and currently has no active neovascularization. What's the



ACETAZOLAMIDE. This drug can be useful for acute reduction of intraocular pressure, if the physician is mindful of systemic considerations.

next step to control the IOP?

In the office setting, with the patient on maximum topical medication, the immediate option would be to reduce IOP with a systemic drug. Although most cases of neovascular glaucoma are refractory to long-term pharmacological treatment, a drug such as acetazolamide can be used as a temporizing measure while the physician plans a more definitive surgical approach.

However, is acetazolamide appropriate in a patient with known CKD? Key considerations include creatinine clearance; hepatic status; and history of epilepsy, drug allergy, or pulmonary disease; as well as other medications the patient may be taking.

Creatinine Clearance

Pharmacology. The following brief pharmacological review may be helpful in considering this case. Oral acetazolamide is 100 percent excreted unchanged, which means that the drug

is eliminated through the kidneys and does not depend on metabolism for inactivation of the drug. Therefore, creatinine clearance (CrCl) directly influences the duration of action. Acetazolamide is reportedly 90 to 98 percent protein bound; this means that 2 to 10 percent of the drug is active and excreted at a given moment, which affects the pharmacodynamics of the drug such as onset of action (1-1.5 hours), peak effect (2-4 hours), and elimination half-life (8-12 hours in healthy adults).^{1,2}

Mechanism of action. Carbonic anhydrase inhibitors, including acetazolamide, impair resorption of HCO_3^- from the kidney's proximal tubule, which osmotically leads to loss of Na^+ and water along with bicarbonate. There is some distal compensation of Na^+ loss, so Na^+ is resorbed from tubular fluid with Cl^- . Because the tubular fluid is negatively charged, K^+ loss occurs, leading to hyperchloremic metabolic acidosis (a decrease in plasma bicarbonate leads to transient metabolic acidosis), hypokalemia, and depleted volume status.

The diuresis associated with acetazolamide may be temporary due to the high number of carbonic anhydrase enzymes in the kidneys; this may require very high doses of the drug to be effective, which also exposes the patient to greater risk of adverse effects. Moreover, some patients develop drug tolerance, which may occur after taking the medication for one to six months. The tolerance is thought to result from up-regulation of carbonic anhydrase activity.¹

Dosage adjustments in CKD. The following dosages are recommended for patients with renal compromise:

- **If CrCl > 50 mL/min:** Use full dose (250 mg four times a day or 500 mg extended-release capsule [e.g., Diamox Sequels] twice daily).
- **If CrCl 10 to 50 mL/min:** Use a half dose (250 mg twice daily).
- **If CrCl < 10 mL/min:** Do not give acetazolamide.
- **If the patient is on hemodialysis:** Use a half dose (250 mg twice daily).
- **If the patient is on peritoneal dialysis:** Use 125 mg daily.³⁻⁵

In patients with end-stage renal

disease, oral acetazolamide has been found to reduce IOP only 50 percent as much as it does in healthy patients.⁶

Hepatic Status

Acetazolamide is contraindicated in patients with liver cirrhosis because it decreases ammonia clearance and increases the risk for hepatic encephalopathy. In patients with mild liver disease, dose adjustment of the drug is not necessary, since acetazolamide is not metabolized by the liver.

Drug interactions. Caution must be exercised for patients taking metformin or high-dose aspirin: Acetazolamide inhibits CYP3A4 enzyme activity and may enhance the adverse effect of these medications. Patients on concomitant metformin and acetazolamide may have an increased risk of developing lactic acidosis and poor glucose control.²

For patients taking concurrent high-dose aspirin and acetazolamide, severe adverse effects have been reported, including coma, anorexia, tachypnea, and even death, likely as a result of acute salicylate intoxication from reduced liver metabolism of salicylate induced by acetazolamide. We recommend avoiding acetazolamide in a patient who is on high-dose aspirin and has renal impairment (CKD).²

Epilepsy

Systemic acetazolamide is occasionally prescribed by neurologists as an adjunct treatment in epilepsy because increased acidosis reduces the spread of seizure. However, acetazolamide may increase serum levels of anti-convulsants such as phenytoin or carbamazepine due to inhibition of CYP3A4 metabolism.¹ Therefore, an ophthalmologist who wishes to use acetazolamide in a patient with a history of epilepsy should do so in consultation with a neurologist or primary care physician.

In addition, caution should be exercised in prescribing acetazolamide to a patient on topiramate, since topiramate also inhibits carbonic anhydrase, which increases the risk of metabolic acidosis as well as kidney stones.¹

Common Clinical Questions

Is it OK to take oral acetazolamide with food?

Yes—food does not delay the rate of absorption of the drug.¹

Does acetazolamide affect the metabolism of oral contraceptives?

No, plasma levels of hormonal contraceptives are not affected by oral acetazolamide, since the drug does not induce CYP3A4 metabolism, so contraception control should still be intact.¹

Is methazolamide adjusted similarly?

Although methazolamide has fewer side effects than acetazolamide and is well tolerated by most patients, methazolamide is not removed by dialysis, and only 25 percent of the drug is excreted unchanged. This indicates that methazolamide involves hepatic metabolism, unlike acetazolamide; therefore, methazolamide is contraindicated in patients with marked renal or hepatic impairment.² Methazolamide is a weaker drug than acetazolamide and is metabolized slowly from the gastrointestinal tract. Methazolamide is 55 percent protein bound and has a later onset of action (2-4 hours), peak effect (6-8 hours), and elimination half-life (14 hours).

1 Patsalos PN, Bourgeois BF (eds). Acetazolamide. In: *The Epilepsy Prescriber's Guide to Antiepileptic Drugs*. Cambridge, U.K.: Cambridge University Press; 2010:1-10.

2 Acetazolamide: drug information. www.uptodate.com/contents/acetazolamide-patient-drug-information. Accessed Jan. 4, 2015.

Pulmonary Disease

Acetazolamide should be used with caution in patients with chronic obstructive pulmonary disease (COPD) because the drug may aggravate respiratory acidosis. It should not be used in a patient who is having an acute COPD exacerbation. However, if a patient has chronic respiratory acidosis with metabolic compensation (mild alkalemia) at baseline, inducing additional metabolic acidosis may be acceptable and may even stimulate respiratory drive.

History of Sulfa Allergy

When patients report a “sulfa allergy,” the clinician should determine whether the patient developed a reaction to a sulfonamide antibiotic or a sulfonamide nonantibiotic drug; the latter category includes carbonic anhydrase inhibitors such as acetazolamide. The important distinction is that sulfonamide antibiotics have structurally different substituents at the N1 and N4 position that may elicit a severe hypersensitivity response, even to the point of anaphylaxis, whereas nonantibiotic sulfonamides lack that structural configuration and, accordingly, are less likely to cause severe reactions. Moreover, cross-reactivity between sulfonamide antibiotics and nonantibiotics is extremely rare.²

If IOP reduction via a systemic route is necessary in a patient with a prior minor allergic reaction to a sulfonamide antibiotic, the use of acetazolamide or methazolamide is permissible with the patient’s informed consent regarding possible risk. However, even though acetazolamide appears to have no specific cross-reactivity with sulfonamide antibiotics, it is contraindicated in patients with prior serious sulfa allergy such as Stevens-Johnson syndrome.

Recommendations

Once it is confirmed that the etiology of the high IOP is not pupillary block and that laser peripheral iridotomy is not indicated, oral acetazolamide can be given with the appropriate adjustments, as long as there are no contraindications, with key systemic consid-

erations mentioned above.

Counseling the patient is important. Encourage the patient to drink additional water and supplement potassium intake with one banana daily. Although kidney stone formation may not necessarily be reduced by diet, certain foods that induce a mild metabolic alkalosis may theoretically increase urine citrate and possibly lower the risk. (Citrate inhibits crystallization of calcium salt.)

If the patient is on hemodialysis or has severe kidney disease, appropriate communication with the nephrologist should be initiated. Monitor for central nervous system disturbances such as fatigue, lethargy, and confusion.

Even though the oral acetazolamide dosing can be adjusted in the short term for patients with renal impairment, the drug may be less effective in lowering IOP in this population. These patients will likely need surgical intervention or cyclophotocoagulation, as indicated, to better control IOP. ■

1 Patsalos PN, Bourgeois BF (eds). Acetazolamide. In: *The Epilepsy Prescriber’s Guide to Antiepileptic Drugs*. Cambridge, U.K.: Cambridge University Press;2010:1-10.

2 Acetazolamide: drug information. www.uptodate.com/contents/acetazolamide-patient-drug-information. Accessed Jan. 4, 2015.

3 Roy LF et al. *Am J Kidney Dis*. 1992;20(6): 650-652.

4 Schwenk MH et al. *Pharmacotherapy*. 1995; 15(4):522-527.

5 Schwenk MH et al. *Adv Perit Dial*. 1994; 10:44-46.

6 Yue CS et al. *J Pharm Pharmaceut Sci*. 2013; 16(1):89-98.

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