Acetazolamide
Acetazolamide Sodium

(ah-set-a-**zole**-a-mide)
Diamox®
Carbonic Anhydrase Inhibitor Diuretic, Antiglaucoma Agent (Systemic Drug)

Prescriber Highlights

- Used sometimes for metabolic alkalosis or glaucoma in small animals and hyperkalemic periodic paralysis (HYPP) in horses.
- Contraindicated in patients with significant hepatic, renal, pulmonary, or adrenocortical insufficiency, hyponatremia, hypokalemia, hyperchloremic acidosis, or electrolyte imbalance.
- Give oral doses with food if GI upset occurs.
- Electrolytes and acid/base status should be monitored with chronic or high dose therapy.
- Monitor with tonometry if using for glaucoma.

Uses / Indications

Acetazolamide has been used principally in veterinary medicine for its diuretic action and its effects on aqueous humor production in the treatment of glaucoma and metabolic alkalosis. It may be useful as an adjunctive treatment for syringomyelia in dogs. Acetazolamide's use in small animals is complicated by a relatively high occurrence of adverse effects.

In horses, acetazolamide is used as a preventive and/or treatment for HYPP.

In humans, the drug has been used as adjunctive therapy for epilepsy and for acute high-altitude sickness.

Pharmacology / Actions

The carbonic anhydrase inhibitors act by a noncompetitive, reversible inhibition of the enzyme, carbonic anhydrase. This reduces the formation of hydrogen and bicarbonate ions from carbonic acid, thereby reducing the availability of these ions for active transport into body secretions.

Pharmacologic effects of the carbonic anhydrase inhibitors include decreased formation of aqueous humor, thus reducing intraocular pressure, increased renal tubular secretion of sodium and potassium and, to a greater extent, bicarbonate, leading to increased urine alkalinity and volume. Acetazolamide has some anticonvulsant activity, which is independent of its diuretic effects (mechanism is not fully understood, but may be due to carbonic anhydrase or a metabolic acidosis effect).

In anesthetized cats, methazolamide did not, but acetazolamide did, reduce the hypoxic ventilatory response. The authors believe this is not a result of carbonic anhydrase inhibition but is instead due to acetazolamide's effects on carotid bodies or type I cells.[1]

Pharmacokinetics

One report states that after a dosage of 22 mg/kg (2-5 times standard dosage), the onset of action is 30 minutes; maximal effects occur in 2 to 4 hours; duration of action is about 4 to 6 hours in small animals.[2] In horses, IV administration of acetazolamide results in a high mean clearance rate (4.5 mL/kg/min) and a short mean residence time (1.71 h). Immediate release formulations show a low oral bioavailability (25%) with maximum concentrations of 1.9 micrograms/mL.[3]

In humans, the drug is well absorbed after oral administration with peak levels occurring within 1 to 3 hours. It is distributed throughout the body with highest levels found in the kidneys, plasma, and erythrocytes. Acetazolamide has been detected in the milk of lactating dogs and it crosses the placenta (in unknown quantities). Within 24 hours of oral tablet administration, an average of 90% of the drug is excreted unchanged into the urine by tubular secretion and passive reabsorption processes.

Contraindications / Precautions / Warnings

Carbonic anhydrase inhibitors are contraindicated in patients with significant hepatic disease (may precipitate hepatic coma), renal or adrenocortical insufficiency, hyponatremia, hypokalemia, hyperchloremic acidosis, or other electrolyte imbalances. This class of drugs should not be used in patients with severe pulmonary obstruction that are unable to increase alveolar ventilation or in those who are hypersensitive to them. Long-term use of carbonic anhydrase inhibitors is contraindicated in patients with chronic, noncongestive, angle-closure glaucoma as further angle closure may occur and the drug may mask the condition by lowering intraocular pressures.

Acetazolamide should be used with caution in patients with severe respiratory acidosis or those with preexisting hematologic abnormalities. Decreased exercise capacity, hypercapnia, and respiratory acidosis may occur in healthy horses during exercise with chronic, high dose administration.[4] Use of acetazolamide with antibacterial sulfonamides or furosemide may cause cross sensitivities.

Adverse Effects

Potential adverse effects that may be encountered include GI disturbances, CNS effects (eg, sedation, depression, weakness, excitement), hematologic effects (eg, bone marrow depression), renal effects (eg, crystalluria, dysuria, renal colic, polyuria), hypokalemia, hyperchloremia, hyperglycemia, hyponatremia, hyperuricemia, hepatic insufficiency, dermatologic effects (eg, rash), and hypersensitivity reactions.

At the dosages used for HYPP in horses, adverse effects are reportedly uncommon.

Reproductive / Nursing Safety

Acetazolamide has been implicated in fetal abnormalities in mice and rats when used at 10 times the recommended dose. Fetal toxicity has been noted when the drug has been used in pregnant humans. In humans, the FDA categorizes this drug as category ***C*** for use during pregnancy (*Animal*

studies have shown an adverse effect on the fetus, but there are no adequate studies in humans; or there are no animal reproduction studies and no adequate studies in humans).

In humans, the manufacturer states that either nursing or the drug must be discontinued if the mother is receiving acetazolamide. Veterinary significance is not clear.

Overdose / Acute Toxicity

Information regarding overdose with this drug was not located. In the event of an overdose, it is recommended to contact an animal poison control center. Monitor serum electrolytes, blood gases, volume status, and CNS status during an acute overdose; treat symptomatically and supportively.

Drug Interactions

The following drug interactions with acetazolamide have either been reported or are theoretical in humans or animals and may be of significance in veterinary patients. Unless otherwise noted, use together is not necessarily contraindicated, but weigh the potential risks and perform additional monitoring when appropriate.

- **ALKALINE URINE**: Drugs where acetazolamide induced alkaline urine may affect their excretion rate: Decreased urinary excretion of **quinidine**, **procainamide**, and **tricyclic antidepressants** may result in toxicity. Increased urinary excretion of **salicylates** and **phenobarbital** may compromise efficacy.
- **ASPIRIN** (or **other salicylates**): Increased risk of acetazolamide accumulation and toxicity; increased risk for metabolic acidosis.
- **CYCLOSPORINE**: Acetazolamide may increase levels.
- **DIGOXIN**: As acetazolamide may cause hypokalemia, increased risk for digoxin toxicity.
- **INSULIN**: Rarely, carbonic anhydrase inhibitors interfere with the hypoglycemic effects of insulin.
- **METHENAMINE COMPOUNDS**: Acetazolamide may negate methenamine effects in the urine.
- **DRUGS AFFECTING POTASSIUM** (eg, **corticosteroids**, **amphotericin B**, **corticotropin**, or **other diuretics**): Concomitant use may exacerbate potassium depletion.

Laboratory Considerations

- **Urine protein**. By alkalinizing the urine, carbonic anhydrase inhibitors may cause false positive results in determining **urine protein** when using bromphenol blue reagent (*Albustix®*, *Albutest®*, *Labstix®*), sulfosalicylic acid (*Bumintest®*, *Exton's® Test Reagent*), nitric acid ring test, or heat and acetic acid test methods.
- **Thyroid function**. Carbonic anhydrase inhibitors may **decrease iodine uptake** by the thyroid gland in hyperthyroid or euthyroid patients and, therefore, lower thyroid hormone levels.
- **Theophylline concentrations**. May interfere with HPLC determination of theophylline.

Dosages

Directions for reconstitution of injection: Reconstitute 500-mg vial with at least 5 mL of sterile water for injection; use within 12 hours after reconstitution. For intravenous use only due to alkaline pH.

- **DOGS**:

Adjunctive therapy of glaucoma, hydrocephalus, or metabolic acidosis (extra-label): 4 – 10 mg/kg PO every 8-12 hours; or IV once.

- **CATS**:

  Adjunctive therapy of glaucoma (extra-label): 6 – 8 mg/kg PO every 8-12 hours.

- **HORSES**: (NOTE: ARCI UCGFS CLASS 4 DRUG)

  Prevention or adjunctive therapy of hyperkalemic periodic paralysis (HYPP) episodes (extra-label): 2 – 3 mg/kg PO every 8-12 hours when diet or environmental adjustments do not control episodes.[5]

Monitoring

- Intraocular pressure tonometry (if used for glaucoma).
- Blood gases if used for alkalosis.
- Serum electrolytes.
- Baseline CBC with differential and periodic retests if using chronically.
- Other adverse effects.

Client Information

- Most common side effect is stomach upset; giving with food may help reduce this effect.
- Contact veterinarian immediately if unusual panting or rapid breathing, weakness, staggering, behavior changes, tremors or seizures (convulsions) are seen.
- Horses must have access to water and food while taking this medication.
- Patients will need ongoing lab tests while on this medicine.

Chemistry / Synonyms

A carbonic anhydrase inhibitor, acetazolamide occurs as a white to faintly yellowish-white,

odorless, crystalline powder with pK_as of 7.4 and 9.1. It is very slightly soluble in water and sparingly soluble in hot water (90ºC-100ºC) and alcohol. Acetazolamide sodium occurs as a white lyophilized solid and is freely soluble in water. The injection has a pH of 9.2 after reconstitution with sterile water for injection.

Acetazolamide may also be known as acetazolam, acetazolamidum, or sodium acetazolamide; many trade names are available.

Storage / Stability

Acetazolamide tablets or un-reconstituted powder for injection should be stored at room temperature.

After reconstitution, the injection is stable for 3 days when refrigerated, but as it contains no preservatives, it should be used within 12 hours. (Package label, Sagent Pharmaceuticals)

Compatibility / Compounding Considerations

Acetazolamide sodium for injection is reportedly physically **compatible** with all commonly used IV solutions and cimetidine HCl for injection.

Compounded preparation stability: Acetazolamide oral suspension stability, when compounded from commercially available tablets, has been published.[6] Triturating twelve (12) 250-mg tablets with 60 mL of *Ora-Plus*® and qs ad to 120 mL with *Ora-Sweet*® (or *Ora-Sweet*® *SF*) yields a 25 mg/mL suspension that retains >90% potency for 60 days stored at both 5ºC and 25ºC. The optimal stability of acetazolamide aqueous liquids is within a pH range of 3 to 5; stability decreases at pH values above 9. Compounded preparations of acetazolamide should be protected from light.

Dosage Forms / Regulatory Status

VETERINARY-LABELED PRODUCTS: None.

The ARCI (Racing Commissioners International) has designated this drug as a class 4 substance.

HUMAN-LABELED PRODUCTS:

Acetazolamide Oral Tablets: 125 mg, 250 mg; generic; (Rx)

Acetazolamide Extended-Release Oral Capsules: 500 mg; *Diamox Sequels*®, generic; (Rx)

Acetazolamide Sodium Injection (lyophilized powder for solution): 500 mg; generic; (Rx)

References / Revisions

Reviewed and updated by Jennifer Davis DVM, PhD, DACVCP, DACVIM (LAIM), and James A. Budde, PharmD, FSVHP, DICVP. Last update August 2017.

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4. Vengust M, et al. Effects of chronic acetazolamide administration on gas exchange and acid-base control in pulmonary circulation in exercising horses. *Equine Vet J.* 2010;42:40-50.
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