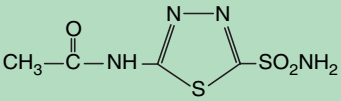
ACETAZOLAMIDE

Therapeutics

Chemical name and structure:

Acetazolamide, *N*-(5-(aminosulfonyl)-1,3,4-thiadiazol-2-yl)-acetamide, is a white to faintly yellowish white odorless crystalline powder with a molecular weight of 222.25.

Although a sulfonamide compound, it is unlike sulfonamide antibiotic compounds. It does not contain an arylamine group at the N4-position, which contributes to allergic reactions associated with sulfonamide antibiotics. The structure of acetazolamide bears some similarity to that of zonisamide. Its empirical formula is $C_4H_6N_4O_3S_2$.



Brand names:

- Acetadiazol; Acetak; Albox; Apo-Acetazolamide; Azol
- Carbinib; Cetamid
- Diamox; Diamox Sequals; Diamox Sustets; Diluran; Diural; Diuramid
- Evamox
- Fonurit
- Glaupax
- Huma-Zolamide
- Ledamox; Lediamox
- Medene
- Optamide
- Renamid
- Stazol; Synomax
- Uramox
- Zolmide

Generics available:

- Yes

Licensed indications for epilepsy:

- Adjunctive treatment of generalized tonic–clonic and partial seizures (UK-SPC)
- Adjunctive treatment of atypical absences, atonic, and tonic seizures (UK-SPC)
- Intermittent therapy of catamenial seizures (UK-SPC)

Licensed indications for non-epilepsy conditions:

- Adjunctive treatment of glaucoma (UK-SPC; FDA-PI)
- Prevention or amelioration of symptoms associated with acute mountain sickness (FDA-PI)

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Nonlicensed use for epilepsy:
- Lennox-Gastaut syndrome

Nonlicensed use for non-epilepsy conditions:
- There are none

Ineffective (contraindicated):
- Acetazolamide is not contraindicated for any seizure type or epilepsy; does not commonly exacerbate seizures

Mechanism of action:
- Potent inhibitor of brain carbonic anhydrase, the enzyme that reversibly catalyses the hydration of CO_2 and the dehydration of carbonic acid
- The carbonic anhydrase inhibition results in an elevation of intracellular CO_2, a decrease of intracellular pH and depression of neuronal activity
- Acetazolamide increases the concentration of weak acids (such as certain antiepileptic drugs, e.g., phenytoin and phenobarbital) into tissue; this may account for part of the efficacy of acetazolamide as add-on therapy
- Tolerance to the effect of acetazolamide often develops, possibly as a consequence of increased carbonic anhydrase production in glial cells

Efficacy profile:
- The goal of treatment is complete remission of seizures
- Onset of action may be rapid and usually within a few days
- Tolerance to the effect of acetazolamide often develops within 1–6 months
- Discontinuation of treatment may re-establish efficacy, making acetazolamide particularly appropriate for intermittent use, such as in catamenial epilepsy
- Acetazolamide is used more commonly as an add-on antiepileptic drug than as monotherapy
- If acetazolamide is ineffective or only partially effective, it can be replaced by or combined with another antiepileptic drug that is appropriate for the patient's seizure type or epilepsy syndrome

Pharmacokinetics

Absorption and distribution:
- Oral bioavailability: >90%
- Food co-ingestion: neither delays the rate of absorption nor reduces the extent of absorption
- Tmax: 2–4 hours
- Time to steady state: 2 days
- Pharmacokinetics: linear

- Protein binding: 90–95% (90% of the drug in the body is bound to tissue carbonic anhydrase)
- Volume of distribution: 0.3 L/kg for total concentration, 1.8 L/kg for free concentration
- Salivary concentrations: it is not known whether acetazolamide is secreted into saliva and whether such concentrations are similar to the unbound levels seen in plasma

Metabolism:
- Acetazolamide is not metabolized

Elimination:
- Half-life values in adults are 10–15 hours
- Renal excretion: 100% of an administered dose is excreted unchanged in urine

Drug interaction profile

Pharmacokinetic drug interactions:
- Interactions between AEDs: effects on acetazolamide:
  - To date, there have been no reports of AEDs affecting the clearance of acetazolamide and affecting acetazolamide plasma levels
- Interactions between AEDs: effects by acetazolamide:
  - Acetazolamide can *increase* carbamazepine plasma levels
  - Acetazolamide can *increase* the free fraction of phenytoin
  - Acetazolamide can *increase* the tissue concentration of other AEDs (e.g., phenytoin and phenobarbital)
  - Acetazolamide can *decrease* the absorption of primidone
- Interactions between AEDs and non-AED drugs: effects on acetazolamide:
  - To date, there have been no reports of other non-AED drugs affecting the clearance of acetazolamide and affecting acetazolamide plasma levels
- Interactions between AEDs and non-AED drugs: effects by acetazolamide:
  - Acetazolamide can *increase* cyclosporin plasma levels
  - Acetazolamide can *decrease* lithium plasma levels

Pharmacodynamic drug interactions:
- It has been suggested that the efficacy of acetazolamide in the treatment of seizures may be due in part to a pharmacodynamic interaction with other antiepileptic drugs
- Acetazolamide prolongs the effects of amphetamines and quinidine
- Anorexia, tachypnea, lethargy, coma, and death have been reported in patients receiving concomitant high-dose aspirin and acetazolamide
- Acetazolamide and sodium bicarbonate in combination increase the risk of renal calculus formation

Hormonal contraception:
- Acetazolamide does not enhance the metabolism of oral contraceptives so as to decrease plasma levels of hormonal contraceptives and, therefore, does not compromise contraception control

Adverse effects

How drug causes adverse effects:
- Carbonic anhydrase inhibition by acetazolamide is likely to be the mechanism responsible for the clinical adverse effects, such as metabolic acidosis, paresthesias, and kidney stones

Common adverse effects:
- Paresthesias, mostly tingling in the fingers and toes
- Drowsiness
- Ataxia
- Blurred vision
- Frequent urination
- Alteration of taste (parageusia), especially for carbonated beverages
- Metabolic acidosis (lowered serum bicarbonate or CO_2)
- Appetite suppression
- Gastrointestinal disturbances (nausea, vomiting, diarrhea)
- Allergic rash

Life-threatening or dangerous adverse effects:
- Very rarely Stevens-Johnson syndrome, toxic epidermal necrolysis, fulminant hepatic necrosis
- Agranulocytosis, aplastic anemia, and other blood dyscrasias

Rare and not life-threatening adverse effects:
- Nephrolithiasis (secondary to decrease in urinary citrate)
- Blood dyscrasias
- Visual changes and transient myopia
- Tinnitus
- Depression
- Loss of libido

Weight change
- Weight loss can occur

What to do about adverse effects:
- Discuss common and severe adverse effects with patients or parents before starting medication, including symptoms that should be reported to the physician
- Discuss symptoms associated with kidney stones
- Some CNS-related adverse effects may be lessened by slow titration, but they may persist at low doses despite slow titration

- Metabolic acidosis is usually compensated, but patients may be treated with oral bicarbonate for CO_2 values of 15–18 mEq/L or less
- If possible, acetazolamide should not be administered to patients on topiramate, zonisamide, or on the ketogenic diet, because these treatments also predispose to metabolic acidosis and to kidney stones
- Patients should be encouraged to drink liberally while on acetazolamide
- Anorexia and weight loss may improve with dosage reduction

Dosing and use

Usual dosage range:

- Adults and children over 12 years of age: 250–1000 mg/day
- Children under 12 years of age: 10–20 mg/kg/day
- Catamenial epilepsy: 8–30 mg/kg/day

Available formulations:

- Tablets: 125 mg, 250 mg
- Extended release capsule: 500 mg
- Parenteral solution: 500 mg powder per vial (requires reconstitution with at least 5 mL of sterile water)

How to dose:

- *For adults and children over 12 years of age*: start treatment with 250 mg/day, once or twice daily; at intervals of 3–7 days increase as needed and as tolerated by 250 mg/day; maintenance dose generally 250 –1000 mg/day
- *Children under 12 years of age*: start treatment with 3–6 mg/kg/day, once or twice daily; at intervals of 3–7 days increase as needed and as tolerated by 3–6 mg/kg/day; maintenance dose generally 10–20 mg/kg/day; doses of 20–30 mg/kg/day may be necessary and are well tolerated
- *Catamenial epilepsy*: acetazolamide has been used in women with catamenial epilepsy both continuously and intermittently during the days of identified seizure exacerbation; maintenance dose generally 8–30 mg/kg/day, doses up to 1000 mg/day may be necessary and are well tolerated

Dosing tips:

- Slow dose titration may delay onset of therapeutic action but enhance tolerability to sedating effects
- Some patients may do very well at relatively low doses of acetazolamide, such as 500 mg/day in adults or 10 mg/kg/day in children; the response to treatment should be assessed at these doses before increasing the dose further
- Acetazolamide may be most effective as add-on therapy and tolerance may develop later when acetazolamide is given as adjunct therapy

- When tolerance has developed, temporary withdrawal of acetazolamide usually restores the previous therapeutic effect
- In patients with catamenial epilepsy, once an effective and well-tolerated dose has been determined, this dose can be administered during the necessary number of days without gradual titration

How to withdraw drug:
- May need to adjust dosage of concurrent medications as acetazolamide is being discontinued, because plasma levels of other drugs may change (see Pharmacokinetic drug interactions section)
- No data are available on potential for withdrawal seizures or symptoms upon rapid discontinuation of acetazolamide; however, rapid discontinuation after chronic use may increase the risk of seizures
- If possible, taper dose over a period of 1–3 months
- In patients receiving intermittent treatment for a few days, such as for catamenial epilepsy, gradual tapering is usually not necessary

Overdose:
- To date, there have been no cases of overdose reported with acetazolamide
- Severe metabolic acidosis could develop, which can usually be corrected by the administration of bicarbonate
- The stomach should be emptied immediately by lavage or by induction of emesis
- Hemodialysis removes acetazolamide from blood and, therefore, serves as a useful procedure in cases of overdose

Tests and therapeutic drug monitoring:
- Serum bicarbonate (CO_2) can be measured before treatment and then periodically, but it is not routine practice to do so
- Other routine laboratory testing is not necessary
- Therapeutic drug monitoring:
  - Optimum seizure control in patients on monotherapy is most likely to occur at acetazolamide plasma concentrations of 10–14 mg/L (45–63 μmol/L)
  - The conversion factor from mg/L to μmol/L is 4.50 (i.e., 1 mg/L = 4.50 μmol/L)
  - The reference range of acetazolamide in plasma is considered to be the same for children and adults, although no data are available to support this clinical practice
  - There are no data indicating the usefulness of monitoring acetazolamide by use of saliva

Other warnings/precautions:
- Patients should be monitored carefully for evidence of an allergic rash
- Patients should be monitored carefully for evidence of kidney stones

- In combination with carbamazepine or oxcarbazepine, there is an increased risk of hyponatremia

Do not use:
- Use with caution in patients undergoing treatments that are associated with an increase in risk of kidney stones, such as topiramate, zonisamide, and the ketogenic diet
- Do not use in patients with hyperchloremic acidosis
- Do not use in patients with cirrhosis because of the risk of severe hyperammonemia
- Use with caution in patients with a history of allergic rash to another medication
- A history of allergic reaction to an antibiotic sulfonamide does not appear to be an absolute contraindication for the use of acetazolamide, because there seems to be no specific cross-reactivity
- Long-term administration of acetazolamide is contraindicated in patients with chronic noncongestive angle-closure glaucoma
- Acetazolamide should not be administered to patients receiving high-dose aspirin – anorexia, tachypnea, lethargy, coma, and death have been reported to occur
- Because of its tendency to cause potassium loss, acetazolamide is contraindicated in Addison disease and adrenal insufficiency

Special populations

Renal impairment:
- Acetazolamide is renally excreted, so the dose may need to be lowered – particularly in patients with a CrCl of < 60 mL/min; the clearance of unbound acetazolamide correlates with the creatinine clearance
- Because acetazolamide can be removed by hemodialysis, patients receiving hemodialysis may require supplemental doses of acetazolamide

Hepatic impairment:
- Acetazolamide is not metabolized and consequently dose adjustment will not be necessary
- Acetazolamide can increase hyperammonemia in patients with liver failure; the mechanism is probably increased renal tubular reabsorption of ammonium secondary to alkalinization of urine

Children:
- Children have an increased metabolic capacity and consequently higher doses on a mg/kg/day basis are usually required to achieve the equivalent therapeutic plasma levels seen in adults

- Age-specific higher incidence of adverse effects of acetazolamide in the pediatric age range has not been described

Elderly:
- Available data on the pharmacokinetics of acetazolamide in elderly patients suggest that they have a higher unbound fraction in the plasma
- The renal clearance of unbound acetazolamide is significantly lower in the elderly, and correlates with the creatinine clearance
- Elderly patients are more susceptible to adverse effects and, therefore, tolerate lower doses better
- Because of an age-related reduction in renal and hepatic function, lower acetazolamide doses may be appropriate
- Invariably the elderly are prescribed drug therapies for concurrent comorbidities and, therefore, the risk of pharmacokinetic interactions is high

Pregnancy:
- Specialist advice should be given to women who are of childbearing potential; they should be informed about the teratogenicity of all antiepileptic drugs and the importance of avoiding an unplanned pregnancy; the antiepileptic drug treatment regimen should be reviewed when a woman is planning to become pregnant
- Rapid discontinuation of antiepileptic drugs should be avoided as this may lead to breakthrough seizures, which could have serious consequences for the woman and the unborn child
- Acetazolamide is classified by the US Food and Drug Administration as risk category C [some animal studies show adverse effects, no controlled studies in humans]
- Use in women of childbearing potential requires weighing potential benefits to the mother against the risks to the fetus
- Use with other antiepileptic drugs in combination may cause a higher prevalence of teratogenic effects than acetazolamide monotherapy
- Taper drug if discontinuing
- Seizures, even mild seizures, may cause harm to the embryo/fetus
- Data on the pharmacokinetic changes of acetazolamide during pregnancy have not been identified

Breast feeding
- Breast milk: in a single case report of a mother taking 1000 mg/day of acetazolamide while breast feeding, acetazolamide concentrations in breast milk were 1.3–2.1 mg/L whereby plasma levels were 5.2–6.4 mg/L. It was calculated that the infant ingested 0.6 mg/day and the infant's plasma levels were 0.2–0.6 mg/L.
- Breastfed infants: acetazolamide plasma levels c/o above case are 4–9% of maternal plasma levels
- If adverse effects are observed recommend bottle feed

The overall place of acetazolamide in the treatment of epilepsy

Acetazolamide is a relatively safe drug which can be used for long periods without serious adverse effects. It is used more often as a second line add-on therapy rather than as monotherapy and in some patients dramatic effects have been observed, and a worthwhile effect has been reported widely in many patients and in differing types of seizures.

Primary seizure types:
- Absence seizures
- Partial seizures

Secondary seizure types:
- Generalized tonic–clonic seizures
- Myoclonic seizures
- Juvenile myoclonic epilepsy
- Catamenial epilepsy

Potential advantages:
- Broad spectrum of seizure protection
- Rapid onset of action
- Associated with few and minor pharmacokinetic interactions
- Favorable adverse event profile with very rare serious adverse effects
- Does not commonly exacerbate seizures

Potential disadvantages:
- Tolerance to the effect of acetazolamide often develops within 1–6 months
- Potential teratogen, but not more than most other antiepileptic drugs

Suggested reading

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