ACETAZOLAMIDE

THERAPEUTICS

Brands
- Diamox, Azomid, AZM, Dazamide, Novo-Zolamide

Generic?
Yes

Class
- Antiepileptic drug (AED), carbonic anhydrase inhibitor

Commonly Prescribed for
(FDA approved in bold)
- **Adjunctive treatment for centrencephalic epilepsies (petit mal, unlocalized)**
- **Acute mountain sickness**
- **Edema due to congestive heart failure or medication**
- **Glaucoma**
- Idiopathic intracranial hypertension (IIH) (pseudotumor cerebrii)
- Episodic ataxias type 1 and 2
- Hemiplegic migraine
- Marfan syndrome
- Sleep apnea

How the Drug Works
- Blocks the carbonic anhydrase enzyme, which is responsible for converting CO_2 and H_2O to bicarbonate. This increases excretion of sodium, potassium, bicarbonate and water, producing alkaline diuresis. In epilepsy, decreases excessive neuronal discharge in CNS due either to inhibition of carbonic anhydrase or slight degree of acidosis. It also reduces production of CSF and aqueous humor

How Long Until It Works
- Seizures – by 2–3 weeks
- IIH – maximum benefit in 4–6 weeks

If It Works
- Seizures – goal is the remission of seizures. Continue as long as effective and well-tolerated. Consider tapering and slowly stopping after 2 years seizure-free, depending on the type of epilepsy
- IIH – monitor visual fields and papilledema and symptoms such as visual obscurations and headache

If It Doesn't Work
Increase to highest tolerated dose
- Seizures – consider changing to another agent, adding a second agent or referral for epilepsy surgery evaluation. When adding a second agent keep in mind the drug interactions that can occur
- IIH – eliminate symptomatic causes such as drugs or toxins, encourage weight loss if patient is obese, consider loop diuretics or topiramate. Lumbar puncture often provides short-term relief of symptoms. For visual loss, optic nerve defenestration or CSF shunting (lumboperitoneal or ventriculoperitoneal) may be needed

Best Augmenting Combos for Partial Response or Treatment-Resistance
- Epilepsy – acetazolamide itself is usually an augmenting agent. Relatively few interactions with other AEDs. Topiramate and zonisamide have similar mechanisms of action, so acetazolamide is not usually combined with these agents
- IIH – furosemide and topiramate may be helpful. Combine with caution due to risk of kidney stone formation

Tests
- Obtain a CBC when starting drug and during therapy. Check bicarbonate, potassium, and sodium levels if symptoms of metabolic acidosis develop

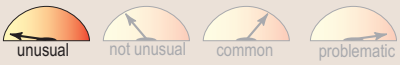
ADVERSE EFFECTS (AEs)

How Drug Causes AEs
- Related to carbonic anhydrase inhibition, which can cause metabolic acidosis and electrolyte imbalances

Notable AEs
- Paresthesias, tinnitus, anorexia, nausea/vomiting, diarrhea, taste alteration, myopia (transient), renal calculi, and photosensitivity

Life-Threatening or Dangerous AEs
- Blood dyscrasias such as agranulocytosis, hemolytic anemia, leukopenia, thrombocytopenia. Hypokalemia. Rash including Stevens Johnson syndrome

Weight Gain
- Unusual



Sedation
- Not unusual

What to Do About AEs
- Lower dose when using for epilepsy or IIH. If AEs are significant, discontinue and change to another agent. Paresthesias may respond to high potassium diets or potassium supplements

Best Augmenting Agents for AEs
- Most AEs cannot be improved by an augmenting agent

DOSING AND USE

Usual Dosage Range
- Epilepsy – 375–1000 mg daily
- IIH – 250–2000 mg daily
- Edema – 250–375 mg qod
- Mountain sickness – 500–1000 mg daily

Dosage Forms
- Tablets: 125, 250 mg. Sustained release 500 mg
- Injection: 500 mg vials

How to Dose
- Epilepsy – Start at 125–250 mg twice daily, with a lower starting dose (250 mg daily) for patients already on other AEDs. Occasionally used at higher doses, but not necessarily more effective
- IIH – Start at 250–500 mg per day in 2 divided doses. Increase as tolerated to 1000 mg/day. Occasionally used at higher doses, depending on tolerability and effect on visual symptoms
- Congestive heart failure – 250–375 mg daily, skipping doses every 2–3 days to maintain effect
- Acute mountain sickness – Start 24–48 hours before ascent and continue for 48 hours or as long as needed to control symptoms. Usual dose 500–1000 mg per day

Dosing Tips
- Citrus juice and fluids may help decrease risk of kidney stone formation. Taking with food can decrease AEs

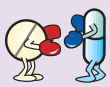
Overdose
- Ataxia, anorexia, nausea, paresthesias, vomiting, tremor and tinnitus. Induce emesis or gastric lavage. Supplement with bicarbonate or potassium as necessary

Long-Term Use
- Safe for long-term use

Habit Forming
- No

How to Stop
- Taper slowly
- Abrupt withdrawal can lead to seizures in patients with epilepsy
- Papilledema or headaches may recur within days to months of stopping

Pharmacokinetics
- Tablets have peak effect at 1–4 hours, with 8–12 hours duration of action. Sustained release tablets have peak effect at 3–6 hours and duration of 18–24 hours. 70–90% protein bound. Not metabolized and excreted unchanged by kidneys



Drug Interactions
- May decrease levels of primidone
- Increases levels of cyclosporine, possibly leading to nephrotoxicity or neurotoxicity
- Concurrent use with salicyclates can increase AEs of both
- May increase effects of amphetamines

Other Warnings/ Precautions
- Carbonic anhydrase inhibitors are sulfonamides. There may be cross-sensitivity with antibacterial sulfonamides

Do Not Use
- Known hypersensitivity to the drug. Depressed potassium or sodium levels, significant kidney or hepatic disease, hyperchloremic acidosis, adrenocortical insufficiency, and suprarenal gland dysfunction

SPECIAL POPULATIONS

Renal Impairment
- Renal insufficiency can lead to increased toxicity. Use with caution

Hepatic Impairment
- Use with caution. Patients with severe disease have an increased risk of bleeding complications

Cardiac Impairment
- Severe hypokalemia causes cardiac arrhythmias. Chronic metabolic acidosis may lead to hyperventilation and decreases left ventricular function – use with caution in patients on beta-blocker or calcium channel therapy

Elderly
- Use with caution

Children and Adolescents
- Safety and effectiveness in the pediatric population is unknown. Suggested daily dose is 8 to 30 mg/kg

Pregnancy
- Category C. Risks of stopping medication must outweigh risk to fetus for patients with epilepsy. Seizures and potential status epilepticus place the woman and fetus at risk and can cause reduced oxygen and blood supply to the womb
- In IIH, consider lumbar puncture as an alternative to medication, especially in the first few months of pregnancy, and monitor closely for visual changes
- Supplementation with 0.4 mg of folic acid before and during pregnancy is recommended

Breast Feeding
- A small percentage is excreted in breast milk. Monitor infant for sedation, poor feeding or irritability

THE ART OF NEUROPHARMACOLOGY

Potential Advantages
- Inexpensive adjunctive medication for epilepsy and useful in the treatment of IIH and episodic ataxias

Potential Disadvantages
- Not a first-line drug in epilepsy or migraine due to ineffectiveness and AEs

Primary Target Symptoms
- Seizure frequency and severity, headache or papilledema in IIH

Pearls
- In epilepsy, appears most effective in children with petit mal epilepsy, but may be effective in patients with grand mal, mixed, or myoclonic seizures
- Acetazolamide is occasionally used for treatment of migraine. Large, double-blind, placebo-controlled trials did not indicate effectiveness
- First-line agent for treatment of episodic ataxias at an average dose of 500–750 per day. Type 2 responds better than type 1 in most cases
- Similar to episodic ataxia type 2, familial hemiplegic migraine type 1 is a channelopathy caused by a mutation of the CACNA1A gene. Case reports suggest acetazolamide can be used to treat hemiplegic migraine
- As a diuretic, increased doses do not increase effect. Results are often improved with alternating days of treatment
- The acetazolamide challenge test is used to decide indications for cerebrospinal fluid shunting

Suggested Reading

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Kossoff EH, Pyzik PL, Furth SL, Hladky HD, Freeman JM, Vining EP. Kidney stones, carbonic anhydrase inhibitors, and the ketogenic diet. Epilepsia 2002;43(10):1168–71.

Reiss WG, Oles KS. Acetazolamide in the treatment of seizures. Ann Pharmacother 1996;30(5):514–9.

Robbins MS, Lipton RB, Laureta EC, Grosberg BM. CACNA1A nonsense mutation is associated with basilar-type migraine and episodic ataxia type 2. Headache 2009;49 (7):1042–6.

ALMOTRIPTAN

THERAPEUTICS

Brands
• Axert, Almogran

Generic?
No

Class
• Triptan

Commonly Prescribed for
(FDA approved in bold)
• **Migraine**

How the Drug Works
• Selective 5-HT1 receptor agonist, working predominantly at the B, D and F receptor subtypes. Effectiveness may be due to blocking the transmission of pain signals from the trigeminal nerve to the trigeminal nucleus caudalis and preventing release of inflammatory neuropeptides rather than just causing vasoconstriction

How Long Until It Works
• 1 hour or less

If It Works
• Continue to take as needed. Patients taking acute treatment more than 2 days/week are at risk for medication overuse headache, especially if they have migraine

If It Doesn't Work
• Treat early in the attack – triptans are less likely to work after the development of cutaneous allodynia, a marker of central sensitization
• For patients with partial response or reoccurrence, add an NSAID
• Change to another agent

Best Augmenting Combos for Partial Response or Treatment-Resistance
• NSAIDs or neuroleptics are often used to augment response

Tests
• None required

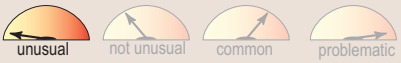
ADVERSE EFFECTS (AEs)

How Drug Causes AEs
• Direct effect on serotonin receptors

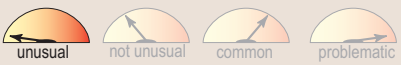
Notable AEs
• Tingling, flushing, sensation of burning, vertigo, sensation of pressure, heaviness, nausea

Life-Threatening or Dangerous AEs
• Rare cardiac events including acute MI, cardiac arrhythmia, and coronary artery vasospasm have been reported with almotriptan

Weight Gain
• Unusual



Sedation
• Unusual



What to Do About AEs
• In most cases, only reassurance is needed. Lower dose, change to another triptan or use an alternative headache treatment

Best Augmenting Agents for AEs
• Treatment of nausea with antiemetics is acceptable. Other AEs improve with time

DOSING AND USE

Usual Dosage Range
• 6.25–12.5 mg

Dosage Forms
• Tablets: 6.25 and 12.5 mg

How to Dose
• Tablets: Most patients respond best at 12.5 mg oral dose. Give 1 pill at the onset of an attack and repeat in 2 hours for a partial response or if headache returns. Maximum 25 mg/day. Limit 10 days per month

Dosing Tips
- Treat early in attack

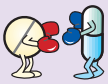
Overdose
- May cause hypertension, cardiovascular symptoms. Other possible symptoms include seizure, tremor, extremity erythema, cyanosis or ataxia. For patients with angina, perform ECG and monitor for ischemia for at least 20 hours

Long-Term Use
- Monitor for cardiac risk factors with continued use

Habit Forming
- No

How to Stop
- No need to taper. Patients who overuse triptans often experience withdrawal headaches lasting up to several days

Pharmacokinetics
- Half-life about 3 hours. Tmax 2.5 hours. Bioavailability is 80%. Metabolized by MAO A enzyme as well as cytochrome P450 (CYP3A4 and CYP2D6) isozymes. 35% protein binding



Drug Interactions
- Monoamine oxidase (MAO) inhibitors may make it difficult for drug to be metabolized
- Theoretical interactions with SSRI/SNRI. It is unclear whether triptans pose any risk for the development of serotonin syndrome in clinical practice
- Minimal increase in concentration with CYP-3A4 inhibitors – no need for dose adjustment

Do Not Use
- Within 2 weeks of MAO inhibitors, or 24 hours of ergot-containing medications such as dihydroergotamine
- Patients with proven hypersensitivity to eletriptan, known cardiovascular disease, uncontrolled hypertension, or Prinzmetal's angina
- Almotriptan was not studied in patients with hemiplegic and basilar migraine
- May worsen symptoms in ischemic bowel disease

SPECIAL POPULATIONS

Renal Impairment
- Concentration increases in those with moderate-severe renal impairment (creatinine clearance less than 30 mL/min). May be at increased cardiovascular risk

Hepatic Impairment
- Drug metabolism may be decreased. Do not use with severe hepatic impairment

Cardiac Impairment
- Do not use in patients with known cardiovascular or peripheral vascular disease

Elderly
- May be at increased cardiovascular risk

Children and Adolescents
- Safety and efficacy have not been established
- Triptan trials in children were negative, due to higher placebo response

Pregnancy
- Category C. Use only if potential benefit outweighs risk to the fetus. Migraine often improves in pregnancy, and other acute agents (opioids, neuroleptics, prednisone) have more proven safety

Breast Feeding
- Almotriptan is found in breast milk. Use with caution

THE ART OF NEUROPHARMACOLOGY

Potential Advantages
- Effective with good consistency and excellent tolerability, even compared to other oral triptans. Less risk of abuse than opioids or barbiturate-containing treatments

Potential Disadvantages
- Cost, and the potential for medication overuse headache. May not be as effective as other triptans

Primary Target Symptoms

- Headache pain, nausea, photo- and phonophobia

Pearls

- Early treatment of migraine is most effective
- Lower AEs compared to other triptans. Good consistency and pain-free response, making it a good choice for patients with anxiety prone to medication side effects
- May not be effective when taken during the aura, or before headache begins
- In patients with "status migrainosus" (migraine lasting more than 72 hours) neuroleptics and dihydroergotamine are more effective
- Triptans were not originally studied for use in the treatment of basilar or hemiplegic migraine
- Patients taking triptans more than 10 days/month are at increased risk of medication overuse headache which is less responsive to treatment
- Chest and throat tightness are usually benign and may be related to esophageal spasm rather than cardiac ischemia. These symptoms occur more commonly in patients without cardiac risk factors

Suggested Reading

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ALTEPLASE

THERAPEUTICS

Brands
- Activase

Generic?
Yes

Class
- Tissue plasminogen activator (TPA), thrombolytic agent

Commonly Prescribed for
(FDA approved in bold)
- **Acute ischemic stroke (AIS)**
- **Acute myocardial infarction (AMI)**
- **Pulmonary embolism (PE)**
- **Restoration of function to central venous access device**

How the Drug Works
- Alteplase is a tissue plasminogen activator. It binds to fibrin in a thrombus and converts the entrapped plasminogen to plasmin, initiating a local fibrinolysis with little systemic effect

How Long Until It Works
- Less than 1 hour, often earlier

If It Works
- After administration, monitor in intensive care – preferably in an acute stroke or cardiac unit

If It Doesn't Work
- Alteplase is not always effective and has risks. After initial monitoring period in intensive care, continue standard AIS, AMI, or PE care

Best Augmenting Combos for Partial Response or Treatment-Resistance
- Not combined with other agents. Use caution with patients already taking anticoagulants or antiplatelet medications

Tests
- Ensure no contraindications are present before administering drug. For all patients with suspected AIS with onset less than 3 hours prior, immediately type and screen, obtain CBC, glucose, coagulation tests, and ensure no intracranial bleeding (usually with head CT)

ADVERSE EFFECTS (AEs)

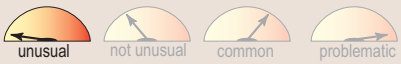
How Drug Causes AEs
- Activating plasminogen increases bleeding risk

Notable AEs
- Superficial bleeding (i.e., at puncture sites), fever, hypotension, dyspnea, nausea, urticaria, and flushing

Life-Threatening or Dangerous AEs
- Internal bleeding (intracranial, GI, GU, or retroperitoneal), anaphylactic reaction, reperfusion arrhythmias, and thrombocytopenia

Weight Gain
- Unusual

Sedation
- Unusual



What to Do About AEs
- Stop infusion for any serious bleeding. Can use fresh frozen plasma if needed

Best Augmenting Agents for AEs
- Most AEs cannot be improved by an augmenting agent

DOSING AND USE

Usual Dosage Range
- 90 mg or less for AIS, 100 mg or less for AMI or PE

Dosage Forms
- Lyophilized powder for injection: 50 mg in 50 mL or 100 mg in 100 mL

How to Dose
- AIS – Give 0.9 mg/kg (not to exceed 90 mg), with 10% of the dose given in the first 1 minute and the remainder infused over 1 hour
- AMI – Give 15 mg as a bolus for all patients. For patients weighing more than 67 kg, then give another 50 mg over 30 minutes and then 35 mg over the next 60 minutes. For patients less than 67 kg, give 0.75 mg/kg over the 30 minutes after the bolus and then 0.50 mg/kg over the next 60 minutes
- PE – 100 mg over 2 hours and restart heparin once partial thromboplastin or thrombin time is less than twice normal

Dosing Tips
- Give alteplase as soon after AIS as possible to achieve best functional outcome once it has been determined that there are no contraindications

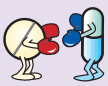
Overdose
- Bleeding complications are common. Treat, if needed, with fresh frozen plasma. Bradycardia, flushing, dyspnea, or hypotension can occur

Long-Term Use
- May be repeated after weeks of previous use if indicated. Not used for prophylaxis

Habit Forming
- No

How to Stop
- Not applicable

Pharmacokinetics
- Rapid hepatic metabolism by hydrolysis. 80% of drug is cleared within 10 minutes after ending infusion



Drug Interactions
- Anticoagulants such as heparin, vitamin K antagonists increase bleeding risk
- Antiplatelet agents such as aspirin, dipyridamole, clopidogrel, and abciximab may increase bleeding risk when given prior to or soon after alteplase therapy
- NSAIDs may increase risk of GI bleed
- Nitroglycerin decreases alteplase concentrations. Avoid using
- Valproate may increase concentrations
- Dopamine may reduce activity and cause particulate formation

Other Warnings/ Precautions
- Cholesterol embolism causing renal failure, pancreatitis, bowel infarction, gangrenous digits, or AMI is a rare complication of thrombolysis

Do Not Use
- Evidence of intracranial hemorrhage or suspected subarachnoid hemorrhage
- Serious head trauma
- History of intracranial bleeding, neoplasm, or arteriovenous malformation
- Active internal bleeding
- Recent intracranial or intraspinal surgery
- Seizure at the onset of stroke
- Bleeding diathesis (current warfarin use, prothrombin time > 15 seconds, heparin use with elevated partial prothrombin time, or platelets count < 100,000 mm^3)
- Uncontrolled hypertension at the time of treatment (greater than 185 systolic or 110 diastolic)

SPECIAL POPULATIONS

Renal Impairment
- No change in dose required

Hepatic Impairment
- Reduce dose and use with caution

Cardiac Impairment
- No known effects

Elderly
- Patients over 75 are more likely to have bleeding complications

Children and Adolescents
- Not studied in children

ALTEPLASE (continued)

Pregnancy

- Category C. Use if potential benefit outweighs risks. Increased risk of hemorrhage when given less than 10 days post-partum

Breast Feeding

- Unknown if present in breast milk, use with caution

THE ART OF NEUROPHARMACOLOGY

Potential Advantages

- Proven treatment for acute stroke

Potential Disadvantages

- Must be used within the acute window. Multiple potential complications

Primary Target Symptoms

- Improving the neurologic disability and reducing disability resulting from ischemic stroke

Pearls

- Effective in improving disability when given in 4.5 hour window. Outcomes are better when treating early. Treat as early as possible after AIS when safe to do so
- In clinical trials use was often followed by anticoagulation with heparin for AMI or AIS
- Control blood pressure and maintain below 185/110 mm Hg during treatment. Blood pressures are often elevated in AIS
- Of 100 patients treated with alteplase for AIS, about 11 of those will recover with minimal or no disability compared with placebo
- Less likely to be effective for larger artery AIS (i.e., carotid occlusion)

Suggested Reading

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