Medical Treatment: Carbonic Anhydrase Inhibitors

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Core Messages

- Oral carbonic anhydrase inhibitors (CAIs) remain a useful choice for intraocular pressure (IOP) lowering.
- CAI dosing must be titrated to the individual.
- CAIs have many potential effects on human physiology and can cause serious complications or even death.
- Systemic CAIs are contraindicated in pregnancy.
- Methazolamide has a better pharmacologic profile than acetazolamide; however, acetazolamide may lower IOP more quickly.

26.1 Are Oral Carbonic Anhydrase Inhibitors Still to Be Used Now That There Are Numerous Effective Topical Medications?

Oral carbonic anhydrase inhibitors (CAIs) were introduced half a century ago for the treatment of glaucoma. Although their use in glaucoma care has been replaced largely by topical therapy, they are still an important therapeutic option in acute situations when topical therapy does not reduce intraocular pressure (IOP) adequately, as a last resort in patients who cannot tolerate topical therapy, or when surgery needs to be delayed or is contraindicated. Therefore, ophthalmologists should remain familiar with the pharmacology of CAIs.

Summary for the Clinician

- Oral CAIs remain useful.
- Ophthalmologists should remain familiar with CAI pharmacology.

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26.2 How Should Oral CAIs Be Dosed?

The ciliary body epithelium's formation of bicarbonate is linked with sodium transport and aqueous secretion. Accumulation of posterior chamber bicarbonate and the subsequent aqueous secretion is inhibited by CAIs. In therapeutic doses, CAIs can reduce up to 50 % of aqueous production and are highly effective for the reduction of IOP in acute situations [1]. For example, if a systemic CAI is given to a patient with an IOP of 40 mmHg (receiving no other ocular hypotensive therapy), the CAI will reduce the outflow pressure of 30 mmHg by 50 % and achieve an IOP of 25 mmHg [2]:

Pretreatment IOP	=40 mmHg
Episcleral venous pressure (EVP)	=10 mmHg
Outflow pressure	=IOP (40) − EVP (10) = 30 mmHg
Posttreatment IOP	=Outflow pressure × 50 % + EVP
	=30 mmHg × 50 % + 10 mmHg
	=25 mmHg

Maximum IOP reduction usually occurs within 2–4 h following oral administration and may last for 6–8 h. When given intravenously, IOP reduction can be observed within 2 min, with a peak effect noted in 10–15 min.

Excess carbonic anhydrase is present in the ciliary processes. It is calculated that 100 times as much enzyme as it is needed for the production of aqueous is present, and therefore the enzyme must be more than 99 % inhibited so as to significantly reduce aqueous flow [1]. However, the maximum CAI dose may not be necessary in every patient because of individual differences in absorption, excretion, metabolism, toxicity, and tolerability. In a nonacute situation, one can start oral CAIs at low doses, such as 25–50 mg of methazolamide twice daily or 125 mg acetazolamide four times daily. The maximum dose is 150 mg methazolamide twice daily, 250 mg acetazolamide tablets four times daily, or 500 mg sustained release acetazolamide capsule twice daily. In acute situations in the clinic, where an urgent reduction of IOP is desirable, usually a single oral dose of 500 mg acetazolamide (i.e., two 250 mg tablets) is administered. In these situations, regular acetazolamide is preferable over the sustained release acetazolamide sequel because a quick therapeutic dose is needed to reduce the IOP on an urgent basis.

Summary for the Clinician

- Individual patients will have different absorption, excretion, metabolism, and side effects with CAIs, and so doses should be individually titrated.
- Start with low doses—methazolamide 25–50 mg b.i.d. or acetazolamide 125 mg q.i.d.
- Maximum dosages are methazolamide 150 mg b.i.d., acetazolamide 250 mg tablets q.i.d., or acetazolamide 500 mg sequel capsule b.i.d.
- In acute situations, intravenous acetazolamide 500 mg can be given with an expected peak effect within 15 min or oral acetazolamide tablets can be given with an expected peak effect in 2–4 h.

26.3 What Are the Toxic Effects of Systemic CAIs?

Commonly reported side effects that may occur shortly after starting systemic CAIs are paresthesias, numbness, and tingling sensations in the hands, feet, and lips, malaise, somnolence, confusion, anorexia, nausea, abdominal discomfort, and an unpleasant taste in the mouth or poor tolerance to carbonated beverages [3]. Some of these side effects are associated with the metabolic acidosis that develops with CAIs or with the inhibitory action of carbonic anhydrase in the central nervous system and gastric mucosa. Reducing CAI dose can reduce these side effects.

The renal *metabolic acidosis* that develops with systemic CAIs may have serious side effects

in children or patients with diabetes mellitus, hepatic insufficiency, renal failure, or chronic obstructive pulmonary disease, and their use in these patients is relatively contraindicated. Metabolic acidosis develops when carbonic anhydrase is inhibited in the kidneys so that bicarbonate is lost in the urine. This loss of bicarbonate alkalinizes the urine, which in turn leads to increased reabsorption of ammonia, a factor to consider in patients with hepatic insufficiency who can then develop hepatic encephalopathy because of increased ammonia levels. CAI-induced metabolic acidosis may exacerbate ketoacidosis in patients with poor control of diabetes or in patients with a preexisting respiratory acidosis. Respiratory acidosis may also be induced in patients with severe chronic pulmonary disease by impairment of carbon dioxide transfer from the pulmonary vasculature to the alveoli in the presence of CAIs [1–3]. In patients with renal failure, the excretion of acetazolamide decreases so that doses must be adjusted for individual creatinine clearance. Patients on hemodialysis for renal failure can use CAIs, but the dose must be dramatically reduced. Although methazolamide is primarily metabolized by the liver, making kidney function less important in determining the dosage, electrolyte imbalance and severe acidosis may still occur in patients with poor renal function.

In healthy patients, *hypokalemia* and metabolic acidosis following the initiation of CAIs tend to be self-limited problems. However, hypokalemia may increase in severity if patients are taking other diuretics, steroids, or adrenocorticotropic hormone (ACTH), or when severe cirrhosis is present. Digitalis toxicity increases in the presence of hypokalemia; therefore, patients on digitalis who have poor renal or liver function, or who are taking other diuretics or steroids concurrently, should have their potassium level monitored periodically [2, 3]. A prudent practice is to fully inform a patient's primary physician about the systemic or topical ocular medications we prescribe to our glaucoma patients, especially those with comorbid conditions and on multiple systemic medications.

Kidney stone formation is not uncommon in patients chronically using systemic CAIs. The exact incidence of renal lithiasis due to CAIs is not well reported, although between 0 and 15 % has been seen after years of use [4, 5]. The stones are usually composed of calcium phosphate, due to the metabolic acidosis and resulting low levels of urinary citrate and high levels of urinary calcium. Ordinarily, urinary citrate forms a soluble complex with calcium, which can otherwise precipitate as an insoluble salt. The risk of kidney stone formation is lower with methazolamide than with acetazolamide. One retrospective case–control series reported the incidence of stones to be 11 times higher in patients using acetazolamide. Continued use after occurrence of a stone was associated with a high risk of recurrent stone formation. However, a history of spontaneous stone formation more than 5 years prior to acetazolamide therapy did not appear to be associated with an increased risk [6]. Very low serum levels of CAI are seen with topical application, and thus far no reports of kidney stones have been reported with their use [3].

All CAIs are members of the sulfonamide family, but CAIs do not contain the structural features that are responsible for the immunological reactions in sulfonamide antibiotics. These features include the N1 heterocyclic ring that is believed to be the immunologic determinant of type I immediate hypersensitivity reactions and reactive metabolites formed at the N4 amino nitrogen responsible for non-type I hypersensitivity responses to sulfonamide antibiotics. Therefore, cross-reactivity between sulfonamide antibiotics and nonantibiotic sulfonamide-containing drugs is unlikely. However, a T-cell-mediated immune response to the parent sulfonamide structure appears to be responsible for hypersensitivity reactions in a small subset of patients. Thus, cross-reactivity remains possible. [7] The most severe form of manifest allergy is Stevens–Johnson syndrome, which can be fatal. It has been recognized that many patients report an allergy to sulfa that is not truly an allergic reaction, but rather a side effect, such as nausea [8]. If systemic CAI is urgently needed, it is worth exploring in depth the kind of reaction the patient previously experienced. It is prudent to instruct patients to report any rashes that break out on the body or angioedema after initiation of CAIs.

Aplastic anemia is a rare but potentially fatal idiosyncratic reaction to CAIs. Some patients may develop isolated neutropenia, thrombocytopenia, or pancytopenia that can recover uneventfully [9]. Routinely obtaining complete blood counts (CBC) are not predictive of this idiosyncratic reaction, which is very rare and not dose related, and therefore, routine CBCs are not recommended. However, patients can be alerted to report unusual epistaxis, bruising, or bleeding of the gums, as possible early signs of thrombocytopenia. There have been no reports of Stevens–Johnson syndrome or blood dyscrasias following use of topical CAIs [3]. However, given that systemic absorption occurs, it is recommended to discuss these possible side effects with patients when initiating topical therapy.

Summary for the Clinician

- Metabolic acidosis and hypokalemia can occur with systemic CAI use. Great caution is advised when prescribing CAIs to patients with poor renal or liver function, COPD, poorly controlled diabetes mellitus, and in those taking other diuretics, digitalis, steroid, or ACTH concurrently. Routinely checking bicarbonate and potassium levels in these patients is prudent.
- Dosing must be adjusted for creatinine clearance in renal insufficiency.
- Hepatic encephalopathy may occur in patients with hepatic insufficiency taking CAIs.
- Nephrolithiasis may occur and the risk is greater with acetazolamide.
- Severe allergic reactions, such as Stevens–Johnson syndrome, may occur.
- Aplastic anemia, a rare but potentially fatal idiosyncratic reaction to CAI, may occur. However, routine measurement of the CBC is not recommended.

26.4 Can CAIs Be Used in Pregnant Women or Pediatric Patients?

Both acetazolamide and methazolamide are classified by the U.S. Federal Drug Agency as category C drugs (meaning that studies in animals have indicated adverse effects to the fetus while no controlled studies in women are available, or neither human nor animal studies are available; the drug should only be given if the potential benefit outweighs risk to fetus). Forelimb deformity has been seen in the offspring of animals given acetazolamide. Sacrococcygeal teratoma and transient renal tubular acidosis in the neonates of women given acetazolamide has also been reported [10, 11]. Systemic CAIs are contraindicated in pregnant women and should be avoided by women of childbearing age who intend to become pregnant. Small amounts of acetazolamide have also been found in breast milk, so nursing mothers should avoid this medication. No teratogenic adverse effects have been reported with topical CAIs; however, there are no studies on their use in pregnant women.

Pediatric doses of systemic CAI are calculated according to body weight. The maximum dose for acetazolamide is 10–15 mg/kg/day divided three to four times daily.

It is recommended that chronic systemic CAI use be avoided or limited to very short periods of time because of the metabolic acidosis that occurs. Growth retardation has been reported in young children (1–6-years-old) receiving long-term CAI therapy for seizure disorders (mean duration of use, 3.5 years) due to metabolic acidosis. Children with chronic metabolic acidosis due to renal tubular disorders and diabetic ketoacidosis have also shown stunted growth [12].

Summary for the Clinician

- Systemic CAIs are contraindicated in pregnancy.
- Contraception is advised if used in women of childbearing age.

- Systemic CAIs should be avoided in children or used only for short periods of time.
- Growth retardation due to metabolic acidosis has been reported in children receiving long-term CAI therapy.

26.5 Can CAIs Be Used in Patients with Sickle Cell Anemia?

Metabolic acidosis increases the chances of red blood cell (RBC) sickling in patients with sickle cell anemia and sickle cell trait. In sickle cell patients with traumatic hyphema, IOP can often be very high, and given that decreased microvascular perfusion can make their optic nerve heads more susceptible to IOP damage, the use of systemic CAIs is often entertained. Sickling of RBCs can make it more difficult for them to pass through the trabecular meshwork, and it can also precipitate a systemic crisis. Use of systemic CAI in patients with sickle cell anemia or trait should be with caution and full discussion of risks.

Summary for the Clinician

- Metabolic acidosis increases the chance of RBC sickling in patients with sickle cell anemia.

26.6 How Does Acetazolamide Differ from Methazolamide?

The two oral CAIs commercially available are acetazolamide and methazolamide. Acetazolamide 250 mg and methazolamide 50 mg equivalently inhibit carbonic anhydrase. However, the greater metabolic acidosis associated with acetazolamide can result in a slightly lower IOP than seen with methazolamide for unknown reasons. Since methazolamide is less bound to plasma protein, a relatively lower dose is needed to produce therapeutic levels of carbonic anhydrase enzyme inhibition within the ciliary processes. Because of the excessive concentration of enzyme within the kidney, renal effects of bicarbonate loss from carbonic anhydrase inhibition may be avoided with a moderate dose of methazolamide. Theoretically, methazolamide has other pharmacological advantages over acetazolamide, such as better gastric absorption and easier access into ocular tissue due to a more favorable partition coefficient. It also has a longer duration of action (half-life equals 14 h or approximately double the half-life of acetazolamide) so that it can be administered twice daily [13]. Acetazolamide is available in a sustained-release (500 mg) form used twice daily. Both acetazolamide and methazolamide are well absorbed after oral administration. Acetazolamide is excreted as an intact drug by the kidney, whereas methazolamide is metabolized by the liver (only 25 % is excreted by the kidney); therefore, the dosage of methazolamide may not have to be adjusted in patients with renal insufficiency [1, 2]. For acute situations, where rapid IOP lowering is desired, the longer onset of action seen with methazolamide makes the drug less useful than acetazolamide.

Summary for the Clinician

- Methazolamide is better tolerated than acetazolamide.
- Methazolamide is less likely to cause a metabolic acidosis.
- Methazolamide is less likely to cause nephrolithiasis.
- Acetazolamide has a faster onset of action.
- A greater metabolic acidosis caused by acetazolamide provides additional IOP reduction.

26.7 Are Systemic and Topical CAI Effects Additive?

Oral CAIs can achieve a lower IOP than topical CAIs. Two proposed reasons may account for the stronger hypotensive effect of systemic CAIs. One, the metabolic acidosis induced by oral CAIs may independently lower IOP. The mechanism for this is unknown. Secondly, in addition to inhibition of carbonic anhydrase isozyme II, which is primarily responsible for aqueous humor production, there may be inhibition of other isozymes that contribute to aqueous production [14, 15]. However, the hypotensive effects of topical and oral CAIs are probably not additive [16]. Therefore, concomitant use of a therapeutic dose of topical and systemic CAI is not warranted. However, individual variation may occur. Patients may be using more than one topical medication so that the topical bioavailability of the drug may be lowered by a washout effect. In patients on suboptimal doses of oral CAI, topical CAI may have an additional effect.

Summary for the Clinician

- Oral CAIs may have a stronger hypotensive effect than topical CAIs.
- Generally, use of systemic and topical CAIs together is probably not warranted.
- Topical CAI may supplement the IOP reducing effect of systemic CAI when patients are on less than a full therapeutic dose of oral CAI.

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