Carbonic Anhydrase Inhibitors

Carbonic anhydrase inhibitors (CAIs) work by reducing aqueous production; both oral and topical formulations are available and have been widely used in children with glaucoma. The topical CAIs are generally second-line medication for children, but might be preferred in small infants and in those with contraindications to beta blockers, alpha agonists, and prostaglandin analogs. CAIs lack the convenience of once-daily drugs, but add well to all other drug classes.

Topical CAIs include dorzolamide 2% and brinzolamide 1% formulations, as well as combination drugs (see Fixed-Dose Combinations below). These drugs are ideally dosed 3 times daily, but practically speaking, usually are prescribed twice daily. As monotherapy, the effect of topical CAIs is modest. In a 3‐month randomized trial of children younger than 6 years, dorzolamide 2% monotherapy was maintained through the study period in 28 of 50 (56%) of children younger than 2 years before switching to open-label combinations of dorzolamide and timolol medications, as prompted by the study protocol (compared to 27 of 35, or 77%, of patients randomized to timolol 0.25% monotherapy). In children aged 2–6 years, dorzolamide 2% monotherapy was maintained in 66 of 85 patients (78%), compared to 35 of 46 (76%) of patients randomized to timolol 0.5% monotherapy.[13] However, the study design included an open-label phase and the mean IOP reduction during monotherapy phase was not reported. As monotherapy, dorzolamide achieved mean IOP reduction of 2.7 $\pm$ 5.3 mm Hg in a small retrospective series,[2] whereas brinzolamide lowered IOP 4–5 mm Hg (16%–20%) in a prospective randomized study.[12] When used in conjunction with other medications, reports of dorzolamide effect vary between about 2 mm Hg and 27.4% reduction from baseline in retrospective studies.[2,16]

Topical CAI therapy is safe and generally well tolerated by children. Burning/stinging on instillation (more commonly with dorzolamide than with brinzolamide), ocular hyperemia, and discharge are the most frequently reported side effects, affecting about 5% of children younger than 2 years and 12% of children aged 2–6 years.[2, 13] The topical CAIs are relatively contraindicated in eyes with impaired corneas or corneal transplant, although they can be used in these eyes if clinically required. Rarely, systemic side effects such as fatigue and bradycardia have been reported.[12] Although both topical and oral CAIs are renally excreted, topical CAIs are generally considered safe even in situations in which oral CAIs would be contraindicated.[17]

Oral CAIs are rarely used as monotherapy in children, rather being reserved for refractory glaucoma cases. The available agents include acetazolamide and methazolamide, with acetazolamide much more widely used in children than methazolamide. Available formulations of acetazolamide include tablets (125 mg and 250 mg) and sustained-release capsules (500 mg). Dosing ranges 10–20 mg/kg/day divided in 2–4 daily doses, best taken

with food. Acetazolamide suspensions must be prepared by a pharmacy. Less information is available on the recommended dosing and effectiveness of methazolamide in children.

When added to topical therapies, the additional IOP-lowering effect of oral CAI ranges 30%–36%[16,18] even when topical CAIs are in use. The pediatric neurology literature offers most of the reports on side-effect frequency and severity because oral acetazolamide is the first-line treatment for idiopathic intracranial hypertension (IIH). Metabolic acidosis and compensatory respiratory alkalosis is a well-recognized adverse effect, but is in general well tolerated and asymptomatic, although infants can demonstrate rapid respiratory rates. Other systemic side effects can include increased risk of renal calculi and hypokalemia. In contrast, paresthesia, gastrointestinal symptoms, loss of appetite, lethargy, and metallic taste can make therapy intolerable to patients.[19] Blood dyscrasias have been associated with long-term acetazolamide exposure in adults, but the incidence in the pediatric population is unknown and the value of routine hematologic screening is uncertain.[20] Oral carbonic anhydrase inhibitors are generally considered relatively contraindicated in patients with sulfonamide allergy, although a retrospective review of patients with self-reported "sulfa allergy" and concurrent acetazolamide use suggests low cross-reactivity.[21]

In summary, topical carbonic anhydrase inhibitors are well tolerated and moderately effective in lowering IOP. They are best dosed 2–3 times daily, can be used in combination with most other drug classes, and can be good first- or second-line drugs in most pediatric glaucomas. Oral CAIs reduce IOP more effectively than topical agents and can be added to topical CAIs when needed, but often produce systemic side effects that limit their long-term use in children.