New medical and surgical interventions have expanded the options available to glaucoma patients. Many choose to begin with medical therapy instead of surgery. As with any treatment, topical glaucoma drops have side effects. A classic example is black adrenochrome deposits in the conjunctiva and cornea with topical epinephrine use. Prescribers must be aware of each agent’s common and rare side effects that may greatly affect a patient’s quality of life. This article reviews some of the side effects associated with commonly used topical antiglaucomatous agents.

**ALPHA-2 ADRENERGIC AGONISTS**

Alpha agonists lower IOP by decreasing the production of aqueous humor. Brimonidine is a commonly used selective alpha-2 adrenergic agonist. In 5% to 9% of patients, brimonidine can cause an acute follicular conjunctivitis 6 to 9 months after treatment initiation. A delayed follicular reaction has been reported after 15 months. The incidence is higher (30–48%) for apraclonidine, another alpha-2 adrenergic agonist.2

Dry mouth is a common side effect of alpha-2 adrenergic agonists, and it can be attributed to a systemic action. Children and older adults may be susceptible to central nervous system effects such as lethargy, apnea, hypotension, and bradycardia from the lipophilic nature of this drug class and its ability to cross the blood-brain barrier.3

Rarely, brimonidine causes a granulomatous uveitis that subsides upon drug cessation. This drug has also been reported to cause ocular lichen planus, diagnosed on conjunctival biopsy, which resolves with topical cyclosporine treatment.4

**BETA BLOCKERS**

Topical beta blockers also lower IOP by decreasing the production of aqueous humor. These agents are known to affect the cardiopulmonary system. Topical beta blockers such as timolol have been shown to decrease resting pulse rate, blood pressure, and spirometry values. Occurrences of severe bradycardia and complete heart block have been reported.5 Effects on the central nervous system such as confusion, fatigue, depression, and hallucinations have also been noted, especially in the elderly. Rarely, patients have reported sexual dysfunction as a side effect.6 A slight adverse effect on blood lipoproteins has also been reported with topical beta blocker use.7 Other rarely reported side effects include masking of hypoglycemia in patients with diabetes and masking of symptoms of thyrotoxicosis.

**CARBONIC ANHyDRASE INHIBITORS**

Like alpha agonists and beta blockers, carbonic anhydrase inhibitors (CAIs) reduce IOP by decreasing the production of aqueous humor. Oral CAIs have been associated with metabolic acidosis, hypokalemia, malaise, anorexia and weight loss, a loss of libido, depression, nausea, and gastrointestinal upset.

Topical CAIs have largely replaced oral CAIs in glaucoma treatment, resulting in far fewer systemic side effects. The two most popular topical CAIs are dorzolamide and brinzolamide. Common side effects of topical CAIs include burning on instillation, hyperemia, blurry vision, and pruritus, all of which are likely caused by the marked acidity (pH 5.5) of the drops.8 The bitter metallic taste that some patients experience may be secondary to drainage from the tear ducts into the mouth, where carbonic anhydrase is inhibited, causing excess bicarbonate in the saliva.

Topical CAIs should be prescribed with caution in patients who have a history of corneal disease because the inhibition of endothelial carbonic anhydrase may lead to corneal edema and irreversible decompensation.9 Severe periorbital dermatitis with scaly, erythematous eyelid skin can occur 4 to 40 weeks after the initiation of dorzolamide treatment.10

A rarely reported side effect of CAIs is bone marrow suppression leading to thrombocytopenia, aplastic anemia, agranulocytosis, pancytopenia, and even death.11 Reversible thrombocytopenia has been reported with topical dorzolamide. Ciliochoroidal effusion may be induced by acetazolamide and lead to a myopic shift and angle-closure episodes.12 Finally, sulfa-related drugs such as acetazolamide have been implicated in causing toxic epidermal necrolysis.13

**PROSTAGLANDIN ANALOGUES**

Prostaglandin analogues (PGAs), which reduce IOP by increasing uveoscleral outflow, may induce hypertrichosis, conjunctival hyperemia, irreversible darkening of the iris, darkening of the periorbital skin, prostaglandin-associated periorbitopathy (PAP), cystoid macular edema (CME), and nongranulomatous anterior uveitis.14 Hypertrichosis typically occurs 6 to 12 months after PGA initiation. Trichiasis requiring epilation has also been reported. Darkening of the iris and periorbital skin are common
Side effects from PGAs may include hypertrichosis, acne, and skin reactions. Latanoprostene bunod has been reported to cause iris cyst formation, bullous epithelial edema, and ciliochoroidal effusion syndrome. Rho-kinase inhibitors, like netarsudil, can cause anterior uveitis, keratitis, and stromal edema. If side effects persist, discontinuation of the drug is recommended.

Conclusions:

- Side effects from PGAs may include hypertrichosis, acne, and skin reactions.
- Latanoprostene bunod can cause iris cyst formation, bullous epithelial edema, and ciliochoroidal effusion syndrome.
- Rho-kinase inhibitors, like netarsudil, can cause anterior uveitis, keratitis, and stromal edema. If side effects persist, discontinuation of the drug is recommended.

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