Clinical and Experimental Vision and Eye Research (2022), 5, 1–3

EDITORIAL

Systemic Medications and Glaucoma, Medications that Increase the Risk of Glaucoma

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With increasing longevity, and the subsequent increase in the number of chronic lifestyle diseases, the increase in the incidence and prevalence of glaucoma is a logical conclusion.

In fact, experts predict that the estimated number of glaucoma patients worldwide will increase to 111.8 million by 2040.[1] However, these projected estimates, and others that predict the global burden of glaucoma blindness often do not take into account the effect of polypharmacy on both, the incidence, and progression of glaucoma. It is therefore essential, not only for the glaucoma surgeon, but also the general physician to be aware of the impact of systemic medications, often used very commonly, on glaucoma incidence and progression.[2-4]

The systemic medications that may modulate the risk for glaucoma may do so through three main pathways.

1. Their impact on aqueous humor outflow facility, and on the pupillary size and lens iris diaphragm thus affecting the aqueous drainage, and intraocular pressure (IOP)
2. Their impact on ocular blood flow, or through modulation of its rheological properties thus affecting optic nerve perfusion
3. Their neuroprotective impact independent of IOP by affecting retinal ganglion cell survival.

Medications that can precipitate, or worsen glaucoma iatrogenic glaucoma, or its worsening may primarily be attributed to the impact of the drug on IOP via the aqueous humor outflow facility.

Angle-Closure Glaucoma

Even though iatrogenic acute angle-closure glaucoma (AACG) is relatively uncommon, it usually presents bilaterally. If not recognized early in its onset, it can cause devastating visual loss. These attacks of pupillary block usually occur due to the impact of the systemic drugs on the lens-iris diaphragm and are seen most often in patients with underlying angle-closure disease. Most of these patients have pre-existing, undiagnosed narrow iridocorneal angles, and present with AACG. A very high index of suspicion and a thorough history taking is critical for identifying these patients. If recognized early in the natural history of disease, visual morbidity can be avoided by promptly discontinuing the drugs and instituting anti-glaucoma drugs for IOP control.

The most common offending agents include the following:

- Anticholinergics
- Adrenergics
- Cholinergics
- Sulfonamides
- Anticoagulants

Mechanism of Action

Anticholinergic drugs cause mydriasis by blocking the parasympathetic muscarinic acetylcholine receptors sphincter muscle of the iris. This results in the pupillary block. Also implicated is the pupillary dilatation through the 5-hydroxytryptamine (5-HT), serotonin receptors, and norepinephrine receptors by selective serotonin reuptake inhibitors, which have a weak anticholinergic effect as well. Botulinum toxin may also cause mydriasis due to the inhibition of the release of acetylcholine at the neuromuscular junction.

Topiramate use may result in supraciliary effusions, lens thickening (which also causes induced myopia), and a forward rotation of the lens-iris diaphragm. All of these contribute to the narrowing of the anterior chamber and angle closure. It is important to remember that, counter-intuitively, the AACG secondary to topiramate is treated with cycloplegia and steroids, unlike other AACGs which are treated by constricting the pupils.

Open-Angle Glaucoma

Summary of systemic medications may increase or decrease the risk of glaucoma.

Open-angle glaucoma (OAG)

Both ocular hypertension (OHT) and secondary OAG following corticosteroid use are known to occur in susceptible individuals. Patients previously diagnosed with glaucoma or with a family history of the disease are the most vulnerable.[5,6] As many as

25–35% of patients develop steroid-induced OHT, with five of hundred being high responders. The latter report an IOP increase of more than 15 mmHg from baseline, with IOP well into the 30s. All routes of drug delivery may result in this increase in IOP including oral, injectable, inhaled, intranasal, cutaneous as well was intra and periocular steroids. Of these, the most potent offenders are topical eye drops, and injected periocular and intravitreal steroids, which can result in both, acute, and chronic IOP increase.[7] Discontinuing the steroid or its replacement by a non-steroidal anti-inflammatory medication, whenever possible, or reducing its potency or frequency may help control the IOP. This usually results in IOP lowering over 4 to 6 weeks. If not, or in case of high IOP at presentation, topical and systemic antiglaucoma medications, or even surgery, may be required.

Mechanism of Action

Corticosteroids cause an increase in the indigestible glycosaminoglycans in the trabecular meshwork because of an inhibition of matrix metalloproteinase inhibitors as well the activation of transforming growth factor-β signaling. This increases the resistance to aqueous outflow and causes a consequent increase in IOP.

Since corticosteroids are prescribed for many diseases conditions, as many as 7% of the population may actually be exposed to their ocular side effects. It is for this reason that communication between those prescribing steroids and eye specialists is critical. Monitoring the IOP in these patients, especially in those with glaucoma, or its family history is imperative.

Various authors have reported a significant relationship between the duration of steroid use and risk IOP elevation and/or steroid-induced glaucoma (SIG). This risk is significantly lesser for oral steroids as compared to topical use, except for patients in the geriatric age group, receiving in excess of 80 mg of hydrocortisone equivalents per day.[8,9]

Similarly, intravenous administration of 1 g of methylprednisolone for 5 days of pulsed therapy in patients of multiple sclerosis may cause a mild IOP elevation, within the normal range. This elevation was seen to persist for a month, with a gradual decrease over the next 2 months following cessation of therapy.[10] Potentially sight-threatening IOP elevation was described in two patients with pre-existing severe uveitis and secondary glaucoma.[11]

Even though intravenous short-duration pulse therapy may be safe for general population, caution is advised in known cases of glaucoma.

Topical use of steroid percutaneous ointments periorbital region can significantly increase the risk of IOP elevation/SIG. The increased risk of glaucoma with the application of the steroid on the eyelids and periorbital region may be attributed to its thinner stratum corneum, higher blood supply, and the consequent higher absorption rate in the region. In fact, atopic glaucoma is identified as a specific disease entity which encompasses the entire clinical spectrum ranging from pure atopic glaucoma to that caused by the steroid treatment of atopic dermatitis.[12]

It is important to note that while potent topical dermatological GCs significantly increase the risk of glaucoma over long-duration use, weaker steroids do not seem to increase the risk of IOP elevation.[13] Even though the evidence in this regard is conflicting, steroid responders, glaucoma patients, and those with a family history of the disease need special attention, especially when the treatment if required for long durations.[14]

Inhaled or nasal steroids may also cause IOP elevation in susceptible patients, especially with high doses and prolonged use for more than 3 months.[8] Various authors have reported the incidence of OHT to be as high as 3.7% in patients using steroid inhalers for asthma.[15,16]

As many as 42% patients were reported to develop SIG after using fluticasone propionate for more than a year.[17] It is important to remember that this risk is seen in patients with a significant family history (documented first-degree relative) of glaucoma. On the other hand, several population-based studies have failed to detect any association between the increased risk of glaucoma and inhaled steroids for respiratory diseases in normal subjects, as well as patients with OHT or glaucoma.[15,18]

SIG is an iatrogenic, open-angle glaucoma secondary to steroid use which can be vision threatening. Given the ubiquitous and often indiscriminate use of steroids in clinical practice, all efforts must be directed at ensuring that IOP is monitored for these patients.

A regular follow-up is especially recommended for children, those with glaucoma, an increased risk of glaucoma, including first-degree relatives of glaucoma patients.

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Received: 12-08-2022;
Accepted: 29-08-2022
doi: 10.15713/ins.clever.88

How to cite this article: Bhartiya S. Systemic Medications and Glaucoma, Part One: Medications that Increase the Risk of Glaucoma. Cli Exp Vis Eye Res J 2022;5(2):1-3.