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Drug induced (toxic) glaucoma

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Glaucoma is the leading cause of irreversible blindness in the world and the second most common cause of blindness overall. The prevalence of glaucoma is approximately 3% of the population worldwide¹. Due to the fact that increasing age is a risk factor for the development of glaucoma, an increase in life expectancy worldwide will be associated with a predicted increase in the prevalence of glaucoma. Similarly, advancements in medicine and an aging population have led to an increase in polypharmacy. Nearly two-thirds of all US adults aged 40–64 and 90% of individuals ≥ 65 years of age have been prescribed 5 or more medications at a time². Unfortunately, when assessing glaucoma patients, physicians may overlook systemic medications and focus solely on the topical medications. However, many systemic drugs have been shown to cause or worsen glaucoma³. Therefore, the rise in polypharmacy and its effect on glaucoma must be better understood in order to decrease the worldwide glaucoma burden.

Drug-induced glaucoma, or toxic glaucoma, is a form of secondary glaucoma that can be distinguished by the mechanism causing the glaucoma: open angle or closed angle glaucoma. The overall incidence of drug-induced glaucoma is unknown.

OPEN ANGLE DRUG-INDUCED GLAUCOMA: **Corticosteroids**

The most common drug that induces open angle glaucoma is corticosteroids. Corticosteroids are used both systemically and locally for their anti-inflammatory properties.

Corticosteroid-induced glaucoma is seen most commonly

after topical drops, periocular, or intraocular injections. However, it can also occur after intranasal, inhalational, systemic use, and dermatological applications⁴.

Systemic treatment usually results in a bilateral increase in intraocular pressure (IOP), while topical treatment usually results in elevated intraocular pressure in the treated eye (although it can be bilateral). Common indications for the use of corticosteroid eye drops include anterior uveitis and post-operative inflammation. Additional uses of cortisone include peri-bulbar and intravitreal injections to treat inflammation and macular edema, respectively. Not surprisingly, intravitreal injections of steroids lead to the highest acute increase in intraocular pressure. This is followed by peri-bulbar injections, and finally topical eye drops. Systemic corticosteroids are also prescribed for many auto-immune diseases and local injections of steroids are often used to manage pain in rheumatological or orthopedic diseases. Although systemic use of steroids is less likely to cause glaucoma, if it does occur, it is not dose or duration dependent⁵.

Pathophysiology of corticosteroid-induced glaucoma

Corticosteroids increase IOP by causing structural and functional effects on the trabecular meshwork outflow system. This occurs through increased production as well as a decreased destruction of the extracellular matrix of the trabecular meshwork. The resulting increase in the deposition of glycosaminoglycans in the trabecular meshwork as well as the reduced activity of matrix metalloproteinases to remove the debris, increases the aqueous outflow resistance, leading to increased IOP⁴.

Epidemiology of corticosteroid-induced glaucoma

The onset and severity of IOP increase depends on the type of corticosteroid use, its frequency, duration, location, as well as patient risk factors. Increased IOP usually manifests 2 to 6 weeks following topical steroid use; however, it may occur earlier, namely among patients with a known history or predisposition for glaucoma prior to corticosteroid application.

Patients in whom an increase in intra-ocular pressure is seen post corticosteroid application, are known as “steroid-responders.” Patients with underlying primary open angle glaucoma (POAG) are at a much higher risk of significant steroid response. Additionally, studies have shown that a family history of glaucoma, diabetes mellitus, and connective tissue diseases such as rheumatoid arthritis can increase the risk of steroid response (**Table 1**). Furthermore, the elderly and children under the age of 6 are more prone to having a steroid response⁴.

Research has demonstrated three levels of response to steroids in the patient population^{6,7}.

- 1) High responders (4-6% of the population)
 - a. IOP above 31 mmHg or an increase of more than 15 mmHg from baseline pressure
- 2) Medium responders (~30-33% of the population)
 - a. IOP between 25-31 mmHg or an increase of 6-15 mmHg from baseline
- 3) Non-responders (~60-66% of the population)
 - a. IOP less than 20 mmHg or a rise of less than 6 mmHg from baseline

Diagnosis and Treatment

Similar to open angle glaucoma, patients with steroid-induced glaucoma are often asymptomatic. Thus, diagnosing steroid-induced glaucoma is the first step in initiating its treatment. The clinician’s awareness of the risks of corticosteroid-induced glaucoma as well as close follow up is important in preventing irreversible glaucoma damage. The suggested follow up should include baseline IOP measurements, followed by subsequent IOP measurements after two weeks, then every 4 to 6 weeks for about three months, and then semi-annually if the initial steroid response has been ruled out⁸.

Discontinuation of the offending agent, in this case the corticosteroid, is the first step. Stopping the medication usually results in a decrease in IOP within 2-4 weeks but can take up to 2 months. The duration of the corticosteroid use may also dictate the time required for the IOP to return to baseline as well as its potential reversibility⁸. If the corticosteroid cannot be completely discontinued, then

titrating to a lower potency corticosteroid or decreasing the frequency may help decrease the IOP. Glaucoma treatment, medical and/or surgical, may also be required if the pressure does not reverse to baseline or glaucoma progression occurs.

Anti-VEGF intravitreal injections

Repetitive intravitreal anti-VEGF injections are frequently used to treat many retinal diseases including, but not limited to, diabetic macular edema, wet age-related macular degeneration, as well as retinal neovascularization due to any ischemic retinal cause.

It is well known that there is an immediate increase in intra-ocular pressure immediately post intra-vitreous injection due to a volume effect⁹. The average IOP within 1 minute of injection has been reported to be >40 mmHg; however, this increase is often times transient and well tolerated by most patients⁹. Nonetheless, serial injections of anti-VEGF can lead to a sustained increase in intra-ocular pressure¹⁰. Recent meta-analysis data showed that the prevalence of sustained IOP increase (> 25 mmHG) post anti-VEGF injection is approximately 5%¹¹. Furthermore, this sustained increase in IOP may be dose related. Several studies have shown that patients receiving 7 or more injections per year have a higher prevalence of sustained IOP rise than those receiving 3 or less¹².

Pathophysiology

Several factors may contribute to the formation of glaucoma post intra-vitreous injections. Chronic elevation in IOP might be related to repeated and ongoing injury to the trabecular meshwork from the high volume, alterations in levels of trabecular meshwork vasodilating modulators such as nitric oxide, toxic effects of drugs or drug delivery, and/or inflammatory damage¹².

Treatment

Careful monitoring for sustained IOP rise after repeated intra-vitreous injections is important to prevent further glaucoma damage. This includes regular IOP monitoring as well as RNFL imaging. Pre-treatment with anti-glaucoma drops may be used to lower intra-ocular pressure immediately post injection as well as 20 minutes after and can be considered as standard procedure in patients with repeated injections. Furthermore, anterior chamber paracentesis can also be performed to lower intra-ocular pressure post-injection¹². Further studies are needed to evaluate whether a lower number of injections using a treat-and-extend protocol and/or a lower sized molecule of anti-VEGF medications can help reduce IOP spikes and sustained IOP elevation post injection¹².

INCIDENCE OF STEROID RESPONSE (%)			
	NON RESPONDERS	MODERATE RESPONDERS	HIGH RESPONDERS
Normal population	60	35	5
Primary open angle glaucoma (POAG)	0	10	90
Family history of POAG	20	50	30

Table 1: Steroid responsiveness in nonglaucomatous, glaucomatous, and glaucoma suspect eyes; adapted from Phulke S et al, 2017

CLOSED ANGLE DRUG-INDUCED GLAUCOMA:

Closed angle glaucoma occurs when there is a physical obstruction of the drainage angle. This can occur through two mechanisms: anterior pulling or posterior pushing of the iris towards the angle.

Anterior pulling angle closure glaucoma occurs when the iris is pulled forward to block the angle through membranous formation and/or synechiae, leading to a reduction in aqueous outflow facility. This is seen in cases of neovascular glaucoma, uveitis, as well as fibrous ingrowth/epithelial downgrowth.

Posterior pushing mechanism occurs when the iris/lens diaphragm is pushed forward with anteriorly-directed force to cause blockage of the angle (**Figure 1**). Risk factors for angle closure include a shallow anterior chamber, short eyes, plateau iris, lens rise or large lens, tumors, and choroidal detachment/effusions. Drug-induced glaucoma is thought to be caused by an anterior rotation of the iris/lens diaphragm and/or pupillary dilation that leads to closure of the drainage angle. Therefore, any systemic medication that dilates the pupils has an increased risk of inducing angle closure in patients with already narrow angles and shallow anterior chambers. Additionally, because these medications are taken orally, they may potentiate bilateral angle closure glaucoma. Patients may be symptomatic and can often complain of eye pain, blurry vision, headache, as well as nausea and vomiting due to the acute rise in IOP.

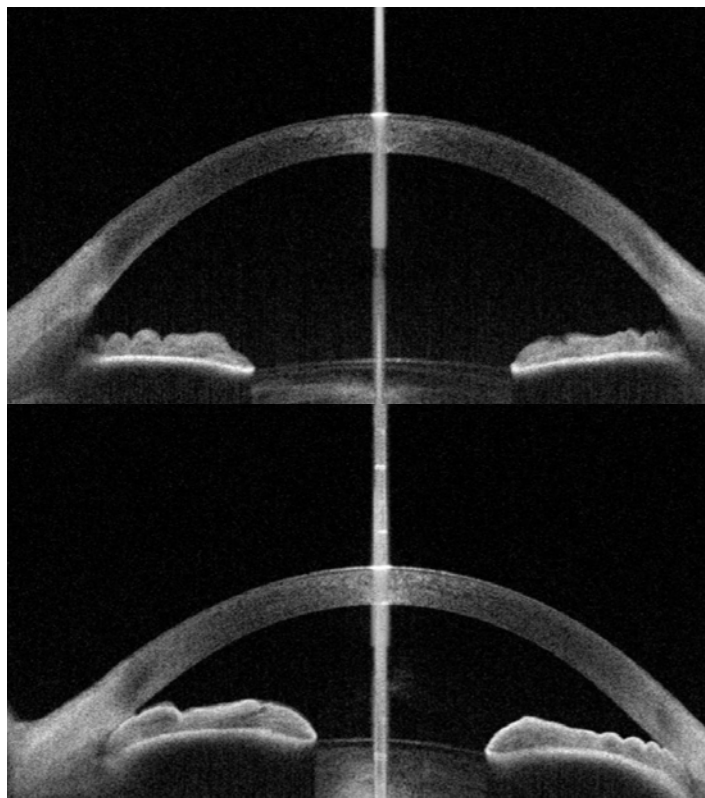


Figure 1: A) Anterior segment OCT of an open angle B) Anterior segment OCT of a closed angle and narrow anterior chamber. Patients with closed angles have a higher risk of acute angle closure in the context of drug-induced glaucoma; photo courtesy of Hady Saheb, MD, MPH.

1) Sulfa-based medications

Sulfa based drugs that have been associated with angle closure glaucoma include acetazolamide, a carbonic anhydrase inhibitor that is used as a diuretic and ironically used in ophthalmology to lower intraocular pressure; hydrochlorothiazide, an anti-hypertensive medication, and cotrimoxazole, an antibiotic often prescribed to treat urinary tract infections. Topiramate, a carbonic anhydrase inhibitor that is a sulfamate-substituted monosaccharide, that is frequently used as an anti-epileptic medication, is most commonly associated with inducing angle closure glaucoma.

Sulfa-based medications are thought to cause angle closure glaucoma through ciliary body edema and expansion that results in zonule laxity. This causes anterior rotation of the iris/lens diaphragm forward with resulting angle closure¹³. This can occur as early as two weeks after initiating the medication¹⁴. Due to its mechanism of action, there is no associated pupillary block and an iridotomy is not effective in treating the angle closure in these cases. Therefore, to treat sulfa-induced angle closure, the medication should be discontinued and the pressure should be treated using medical and or surgical therapy. Studies involving case reports have shown that if identified and treated early, discontinuation of the medication may lead to an improvement of intraocular pressure within hours or days, thereby preventing further glaucoma damage¹⁴.

2) Antidepressants

Fluoxetine, paroxetine, fluvoxamine (all selective serotonin reuptake inhibitors) and venlafaxine (a serotonin and noradrenaline reuptake inhibitor) have been associated with angle-closure glaucoma. The exact mechanism of angle closure with these medications is not known, however, it is thought to be due to the anticholinergic effects of these medications and/or pupil dilation from the increased level of serotonin. The acute angle closure can occur soon after starting these medications as well as after several days¹⁵. Treatment of acute angle closure in these cases requires discontinuation of the antidepressant and the performing of laser peripheral iridotomy to remove any component of pupillary block.

3) Antihistamines

Antihistamine medications such as ranitidine are H1 or H2 receptor antagonists that are used to treat allergies including allergic conjunctivitis. They have a weak anticholinergic effect that induces pupillary dilation and may induce angle closure glaucoma in susceptible patients¹⁵. Treatment of the glaucoma requires discontinuation of the medication and the lowering of the intraocular pressure through laser peripheral iridotomy and/or topical glaucoma medications.

4) Anticholinergic agents

Anticholinergic agents such as atropine and disopyramide are used to treat cardiac arrhythmias. The anticholinergic effect of these medications induces pupillary mydriasis and subsequent pupillary block and angle closure glaucoma in

at-risk patients¹⁵. Treatment of the glaucoma requires discontinuation of the medication and the lowering of the intraocular pressure through laser peripheral iridotomy and/or topical glaucoma medications.

5) Anticoagulants

Warfarin and other anticoagulants can increase the risk of hemorrhagic choroidal detachments (spontaneous or post-traumatic) that can lead to posterior pushing of the lens/iris diaphragm forward, leading to angle closure glaucoma¹⁵. Treatment requires discontinuation of the anti-coagulant, if possible, in addition to medical glaucoma therapy. Drainage of the choroidal hemorrhage may be indicated in certain cases. Since there is no associated

pupillary block, peripheral iridotomy is ineffective in the management of the acute attack.

CONCLUSION

Characteristic optic nerve damage due to glaucoma, with or without elevated intra-ocular pressure, cannot be differentiated by its mechanism. Therefore, secondary drug-induced glaucoma can mimic primary glaucoma (angle closure or open angle). Additionally, as noted previously, patients with drug-induced glaucoma can be symptomatic or asymptomatic. Therefore, when assessing a patient for potential glaucoma, it is imperative that the physician review the complete list of the patient's medications paying careful attention to those that may induce glaucoma in order to properly manage the disease.

DRUG CLASS	EXAMPLE OF DRUG	MECHANISM OF GLAUCOMA	TREATMENT
Corticosteroids	Dexamethasone Prednisone	Open angle glaucoma - Increasing resistance of outflow pathway	Withdrawing agent +/- medical/and or surgical therapy
Anti-VEGF	Bevacizumab Ranibizumab Aflibercept	Open angle glaucoma -Damage to the trabecular meshwork over repeated injections	Pre injection lowering of IOP with topical glaucoma medications and/or anterior chamber paracentesis
Sulfa based drugs	Acetazolamide Topiramate	Angle closure glaucoma- Ciliary body and choroidal effusions leading to anterior rotation of the lens/iris diaphragm	Withdrawing agent +/- medical/and or surgical therapy
Antidepressants	Fluoxetine Paroxetine Fluvoxamine Venlafaxine	Angle closure glaucoma- Pupillary block	Withdrawing agent and laser peripheral iridotomy +/- medical glaucoma therapy
Antihistamines	Cimetidine Ranitidine	Angle closure glaucoma- Pupillary block	Withdrawing agent and laser peripheral iridotomy +/- medical glaucoma therapy
Anticoagulant	Warfarin	Angle closure glaucoma- Anterior rotation of lens/iris diaphragm	Withdrawing agent + medical +/-surgical therapy

Table 2: Drug classes and their impact on glaucoma; courtesy of Dima Kalache, MD

References

1. Flaxman, S. R. et al. Global causes of blindness and distance vision impairment 1990–2020: A systematic review and meta-analysis. *Lancet Glob. Health* 5(12), e1221–e1234 (2017).
2. Charlesworth CJ, Smit E, Lee DS, Alramadhan F, Odden MC. Polypharmacy among adults aged 65 years and older in the United States: 1988–2010. *J Gerontol A Biol Sci Med Sci*. 2015;70:989–95.
3. Ah-Kee, Elliott Yann et al. "A review of drug-induced acute angle closure glaucoma for non-ophthalmologists." *Qatar medical journal* vol. 2015,1 6. 10 May. 2015, doi:10.5339/qmj.2015.6
4. Feroze KB, Khazaeni L. Steroid Induced Glaucoma. [Updated 2022 Mar 1]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK430903/>
5. Godel V, Feiler-Ofry V, Stein R. Systemic steroids and ocular fluid dynamics. II. Systemic versus topical steroids. *Acta Ophthalmol (Copenh)* 1972;50(5):664–676
6. Becker B. Intraocular pressure response to topical corticosteroids. *Invest Ophthalmol Vis Sci*. 1965 Apr;4:198–205
7. Armaly MF. Statistical attributes of the steroid hypertensive response in the clinically normal eye.I. The demonstration of three levels of response. *Invest Ophthalmol Vis Sci*. 1965 Apr;4:187–197
8. Espildora J, Vicuna P, Diaz E. Cortisone-induced glaucoma: a report on 44 affected eye. *J Fr Ophthalmol*. 1981;4(6-7):503–508.
9. Frenkel, R. E., Mani, L., Toler, A. R. & Frenkel, M. P. Intraocular pressure effects of pegaptanib (Macugen) injections in patients with and without glaucoma. *Am. J. Ophthalmol*. 143, 1034–1035 (2007).
10. Good, T. J., Kimura, A. E., Mandava, N. & Kahook, M. Y. Sustained elevation of intraocular pressure after intravitreal injections of anti-VEGF agents. *Br. J. Ophthalmol*. 95, 1111–1114 (2011).
11. Zhou Y, Zhou M, Xia S, et al. Sustained elevation of intraocular pressure associated with intravitreal administration of anti-vascular endothelial growth factor: a systematic review and meta-analysis. *Sci Rep*. 2016;6:39301.
12. Levin, Ariana M. MD*; Chaya, Craig J. MD*; Kahook, Malik Y. MD†; Wirosko, Barbara M. MD. FARVO* Intraocular Pressure Elevation Following Intravitreal Anti-VEGF Injections: Short- and Long-term Considerations, *Journal of Glaucoma: December 2021 - Volume 30 - Issue 12 - p 1019-1026*
13. Fan JT, Johnson DH, Burk RR. Transient myopia, angle-closure glaucoma, and choroidal detachment after oral acetazolamide *Am J Ophthalmol* 1993 Jun; 115 (6): 813-4
14. Fraunfelder FW, Fraunfelder FT, Keates EU. Topiramate associated acute, bilateral, secondary angle-closure glaucoma. 81. *Ophthalmology* 2003.
15. Tripathi et al, Drug Induced Glaucomas Mechanism and Management. *Drug Safety* 2003; 26 (11): 749-767
16. Phulke S, Kaushik S, Kaur S, Pandav SS. Steroid-induced Glaucoma: An Avoidable Irreversible Blindness. *J Curr Glaucoma Pract*. 2017;11(2):67-72. doi:10.5005/jp-journals-10028-1226