Chapter 65: Glaucoma

INTRODUCTION

- *Glaucomas* are ocular disorders that lead to an optic neuropathy characterized by changes in the optic nerve head (optic disc) that is associated with loss of visual sensitivity and field.

PATHOPHYSIOLOGY

- There are two major types of glaucoma: *primary open-angle glaucoma* (POAG) or ocular hypertension, which accounts for most cases and is therefore the focus of this chapter, and *primary angle closure glaucoma* (PACG). Either type can be a primary inherited disorder, congenital, or secondary to disease, trauma, or drugs.
- In POAG, the specific cause of optic nerve damage is unknown. Increased intraocular pressure (IOP) was historically considered to be the sole cause. Additional contributing factors include increased susceptibility of the optic nerve to ischemia, excitotoxicity, autoimmune reactions, and other abnormal physiologic processes.
- Although IOP is a poor predictor of which patients will have visual field loss, the risk of visual field loss increases with increasing IOP. IOP is not constant; it changes with pulse, blood pressure, forced expiration or coughing, neck compression, and posture. IOP demonstrates diurnal variation with a minimum pressure around 6 PM and a maximum pressure upon awakening.
- The balance between the inflow and outflow of aqueous humor determines IOP. Inflow is increased by β-adrenergic agents and decreased by α_2- and β-adrenergic blockers, dopamine blockers, carbonic anhydrase inhibitors (CAIs), meltatonin-1 agonists, and adenylate cyclase stimulators. Outflow is increased by cholinergic agents (eg, pilocarpine), which contract the ciliary muscle and open the trabecular meshwork, and by prostaglandin analogues and β- and α_2-adrenergic agonists, which affect uveoscleral outflow.
- Secondary OAG has many causes, including exfoliation syndrome, pigmentary glaucoma, systemic diseases, trauma, surgery, ocular inflammatory diseases, and drugs. Secondary glaucoma can be classified as pretrabecular (normal meshwork is covered and prevents outflow of aqueous humor), trabecular (meshwork is altered or material accumulates in the intertrabecular spaces), or posttrabecular (episcleral venous blood pressure is increased).
- Many drugs can increase IOP (**Table 65-1**). The potential to induce or worsen glaucoma depends on the type of glaucoma and on whether it is adequately controlled.
- PACG occurs when there is a physical blockage of the trabecular meshwork, resulting in increased IOP.

TABLE 65-1

Drugs That May Induce or Potentiate Increased Intraocular Pressure

Open-angle glaucoma
Ophthalmic corticosteroids (high risk)
Systemic corticosteroids
Nasal/Inhaled corticosteroids
Fenoldopam
Ophthalmic anticholinergics
Succinylcholine
Vasodilators (low risk)
Cimetidine (low risk)
Closed-angle glaucoma
Topical anticholinergics
Topical sympathomimetics
Systemic anticholinergics
Heterocyclic antidepressants
Low-potency phenothiazines
Antihistamines
Ipratropium
Benzodiazepines (low risk)
Theophylline (low risk)
Vasodilators (low risk)
Systemic sympathomimetics (low risk)
CNS stimulants (low risk)
Serotonin-selective reuptake inhibitors
Imipramine
Venlafaxine
Topiramate
Tetracyclines (low risk)
Carbonic anhydrase inhibitors (low risk)
Monoamine oxidase inhibitors (low risk)
Topical cholinergics (low risk)

CLINICAL PRESENTATION

- POAG is bilateral, often asymmetric, progresses slowly, and is usually asymptomatic until onset of substantial visual field loss. Central visual acuity is maintained, even in late stages.
- Patients with PACG typically experience intermittent prodromal symptoms (eg, blurred or hazy vision with halos around lights and, occasionally, headache). Acute episodes produce symptoms associated with a cloudy, edematous cornea; ocular pain; nausea, vomiting, and abdominal pain; and diaphoresis.

DIAGNOSIS

- POAG is confirmed by the presence of characteristic optic disc changes and visual field loss, with or without increased IOP. *Normal tension glaucoma* refers to disc changes, visual field loss, and IOP less than 21 mm Hg (2.8 kPa). *Ocular hypertension* refers to IOP greater than 21 mm Hg (2.8 kPa) without disc changes or visual field loss.
- PACG is usually visualized by gonioscopy. IOP is generally markedly elevated (eg, 40–90 mm Hg [5.3–12 kPa]) when symptoms are present. Additional signs include hyperemic conjunctiva, cloudy cornea, shallow anterior chamber, and occasionally edematous and hyperemic optic disc.

TREATMENT OF OCULAR HYPERTENSION AND OPEN-ANGLE GLAUCOMA

- Goal of Treatment: The goal is to preserve visual function by reducing IOP to a level at which no further optic nerve damage occurs.
- Treat ocular hypertension if the patient has a significant risk factor such as IOP greater than 25 mm Hg (3.3 kPa), vertical cup:disc ratio greater than 0.5, or central corneal thickness less than 555 µm. Additional risk factors to be considered include family history of glaucoma, black, Latino/Hispanic ethnicity, severe myopia, and presence of only one eye. The goal of therapy is to lower IOP by 20%–30% from baseline to decrease the risk of optic nerve damage.
- Treat all patients with elevated IOP and characteristic optic disc changes or visual field defects. An initial target IOP reduction of 25%–30% is desired in patients with POAG.
- Initiate drug therapy in a stepwise manner (**Figure 65-1**), starting with lower concentrations of a single well-tolerated topical agent (**Table 65-2**). Historically, β-blockers (eg, **timolol**) were the treatment of choice provided no contraindications existed.
- Newer agents are also suitable for first-line therapy. Prostaglandin analogs (eg, **latanoprost**, **bimatoprost**, and **travoprost**) offer once-daily dosing, better IOP reduction, good tolerance, and availability of lower-cost generics. **Brimonidine** and topical CAIs are also suitable for first-line therapy.
- If more than one agent is needed, fixed combination products reduce the number of daily doses, which might improve adherence and prevent washout effect seen when a second medication is administered too soon after the initial medication. They also reduce exposure to ophthalmic preservatives.
- **Pilocarpine** is used as third-line therapy because of adverse events or reduced efficacy as compared with newer agents.
- **Carbachol**, **dipivefrin**, topical cholinesterase inhibitors, and oral CAIs (eg, **acetazolamide**) are used as last-resort options after failure of less toxic combination options.
- **Netarsudil** is the first approved Rho kinase inhibitor. Efficacy appears to be similar to that of β-blockers. It may be used in combination therapy.
- Surgical procedures such as laser trabeculoplasty or surgical trabeculectomy can be considered when drug therapy fails, is not tolerated, or is excessively complicated. Antiproliferative agents such as **fluorouracil** and **mitomycin C** are used to modify the healing process and maintain patency.

FIGURE 65-1

Algorithm for the pharmacotherapy of open-angle glaucoma.

(CAI, carbonic anhydrase inhibitor.)

image

TABLE 65-2

Topical Drugs Used in the Treatment of Open-Angle Glaucoma

Drug	Pharmacologic Properties	Common Brand Names/Generic	Dose Form	Strength (%)	Usual Dose[a]	Mechanism of Action

β-Adrenergic blocking agents						
Betaxolol	Relative β_1 selective	Generic	Solution	0.5	One drop twice a day	All reduce aqueous production of ciliary body
		Betoptic-S	Suspension	0.25	One drop twice a day	
Carteolol	Nonselective, intrinsic sympathomimetic activity	Generic	Solution	1	One drop twice a day	
Levobunolol	Nonselective	Betagan/Generic	Solution	0.25, 0.5	One drop twice a day	
Metipranolol	Nonselective	OptiPranolol	Solution	0.3	One drop twice a day	
Timolol	Nonselective	Timoptic, Betimol, Istalol/Generic	Solution	0.25, 0.5	One drop every day—one to two times a day	
		Timoptic-XE/Generic	Gelling solution	0.25, 0.5	One drop every day[a]	
Adrenergic agonists						
α_2-Adrenergic agonists						
Apraclonidine	Specific α_2-agonists	Iopidine	Solution	0.5, 1	One drop two to three	Both reduce aqueous humor production; brimonidine known to also increase uveoscleral outflow; only

					times a day	brimonidine has primary indication
Brimonidine		Alphagan P 0.1/Generic 0.2, 0.15	Solution	0.2, 0.15, 0.1	One drop two to three times a day	
Cholinergic agonists direct acting						
Carbachol	Direct and indirect acting	Carboptic, Isopto Carbachol	Solution	1.5, 3	One drop two to three times a day[a]	All increase aqueous humor outflow through trabecular meshwork
Pilocarpine	Direct acting	Isopto Carpine, Pilocar/Generic	Solution	1, 2, 4	One drop two to three times a day[a]	
					One drop four times a day	
Cholinesterase inhibitor						
Echothiophate	Indirect acting cholinesterase inhibitor	Phospholine Iodide	Solution	0.125	Once or twice a day	
Carbonic anhydrase inhibitors						
Topical						
Brinzolamide	Carbonic anhydrase type II inhibition	Azopt	Suspension	1	Two to three times a day	All reduce aqueous humor production of ciliary body
Dorzolamide		Trusopt/Generic	Solution	2	Two to three times a	

					day	
Systemic						
Acetazolamide		Generic	Tablet	125 mg, 250 mg	125–250 mg two to four times a day	
		Injection	500 mg/vial	250–500 mg		
		Diamox Sequels	Capsule	500 mg	500 mg twice a day	
Methazolamide		Generic	Tablet	25 mg, 50 mg	25–50 mg two to three times a day	
Prostaglandin analogs						
Latanoprost	Prostanoid agonist	Xalatan/Generic	Solution	0.005	One drop every night	Increases aqueous uveoscleral outflow and to a lesser extent trabecular outflow
Latanoprostene Bunod	Prostanoid agonist	Vyzulta	Solution	0.024	One drop every night	
Bimatoprost	Prostamide agonist	Lumigan 0.01/Generic 0.03	Solution	0.01, 0.03	One drop every night	
Travoprost	Prostanoid agonist	Travatan Z/GenericTravoprost	Solution	0.004	One drop every night	
Tafluprost	Prostanoid agonist	Zioptan	Preservative free solution	0.0015	One drop every night	

Rho kinase inhibitor						
Netarsudil	Rho kinase inhibitor	Rhopressa	Solution	0.02	One drop every night	
Combinations						
Timolol–dorzolamide		Cosopt Generic	Solution	Timolol 0.5/Dorzolamide 2	One drop twice daily	
Timolol–brimonidine		Combigan	Solution	Timolol 0.5/Brimonidine 0.2	One drop twice daily	
Brinzolamide–brimonidine		Simbrinza	Suspension	Brinzolamide 1/Brimonidine 0.2	One drop three times daily	
Netarsudil-latanoprost		Rocklatan	Solution	Netarsudil 0.02/Latanoprost 0.005	One drop every night	

[a]Use of nasolacrimal occlusion will increase the number of patients successfully treated with longer dosage intervals.

TREATMENT OF CLOSED-ANGLE GLAUCOMA

- Acute angle-closure crisis (AACC) with high IOP requires rapid reduction in IOP. Iridectomy is the definitive treatment producing a hole in the iris that permits aqueous humor flow to move directly from the posterior to the anterior chamber.
- Drug therapy of an acute attack typically consists of a miotic (eg, pilocarpine), secretory inhibitor (eg, β-blocker, α_2-agonist, latanoprost, or CAI), or prostaglandin agonist.
- Osmotic agents are used to rapidly decrease IOP. Examples include oral **glycerin**, 1–2 g/kg, and **mannitol**, 1–2 g/kg IV.
- Topical corticosteroids can be used to reduce ocular inflammation and synechiae.

EVALUATION OF THERAPEUTIC OUTCOMES

- Successful outcomes require identifying an effective, well-tolerated regimen; closely monitoring therapy; and patient adherence. Whenever possible, therapy for open-angle glaucoma should be started as a single agent in one eye to facilitate evaluation of drug efficacy and tolerance. Many drugs or combinations may need to be tried before the optimal regimen is identified.

- Monitoring therapy for POAG should be individualized. Assess IOP response every 4–6 weeks initially, every 3–4 months after IOPs become acceptable, and more frequently if therapy is changed. Visual field and disc changes are monitored annually, unless glaucoma is unstable or worsening.
- There is no specific target IOP because the correlation between IOP and optic nerve damage is poor. Typically, a reduction of 25%–30% is desired.
- The target IOP also depends on disease severity and is generally less than 21 mm Hg (2.8 kPa) for early visual field loss or optic disc changes, with progressively lower targets for greater levels of glaucomatous damage. Targets as low as less than 10 mm Hg (1.3 kPa) are desired for very advanced disease, continued damage at higher IOPs, normal-tension glaucoma, and pretreatment pressures in the low to middle teens.
- Monitor medication adherence because it is commonly inadequate and a cause of therapy failure.

See Chapter 110, Glaucoma, authored by Richard G. Fiscella, Timothy S. Lesar, Ohoud A. Owaidhah, and Deepak P. Edward, for a more detailed discussion of this topic.