# Ocular Hypotensives

⇒ Targeted at decreasing IOP.

⇒ Basic mechanism of action: (1) reduce the production of aqueous humor (2) increase aqueous humor outflow without reducing production (3) induce alteration of both physiologic pathways on ocular fluid dynamics

## SYSTEMIC hypotensive therapy for glaucoma

1. Osmotic agents:
   - Increase plasma osmolality → promotes diffusion of water from intraocular fluids back into plasma
   - Efficacy reduced in the face of intraocular inflammation
   - Withhold water from patient for 4 hours to produce desired effect

   a) Mannitol
   b) Glycerin

2. Carbonic anhydrase inhibitors (CAI)
   - Carbonic anhydrase catalyzes $CO_2 + H_2O <=> HCO_3^- + H^+$
   - In ciliary body: Formation of bicarbonate moves $Na^+$ and $H_2O$ into the eye, forming **aqueous humor**
   - CAI decrease aqueous humor formation
   - Used in long term treatment in humans
   - Side Effects: gastrointestinal disturbances (eg, anorexia, vomiting, diarrhea), increased diuresis, malaise, and panting secondary to metabolic acidosis, hypokalemia

   a) Dichlorphenamide
   b) Acetazolamide
   c) Methazolamide

## TOPICAL hypotensive therapy for glaucoma

1. Cholingergic agents:
   - Contraction of the ciliary body musculature → leading to miosis and decreased resistance of aqueous humor passage through the outflow pathways
   - Direct and indirect indirect-acting parasympathomimetic agents
     - Direct: acts directly on cholingergic receptor
     - Indirect: Inhibit acetylcholinesterase (AChE), resulting in an accumulation of acetylcholine at receptor sites

   a) Pilocarpine
   b) Carbachol
   c) Demecarium bromide

2. Adrenergic agents
   a) **Agonists:** Epinephrine and dipivalyl epinephrine
      - Mechanism of action not completely understood - reduce formation of aqueous humor and increase aqueous outflow
      - Mediated by **a**2 –adrenergic receptors and is correlated with increased cyclic adenosine monophosphate (cAMP) production by the trabecular meshwork

2. **Agonist:** Apraclonidine
   - Stimulates **a**2 -receptors on the nonpigmented ciliary epithelium to inhibit adenylate cyclase activity. Impairing conversion of adenosine triphosphate (ATP) to cAMP and production of aqueous humor
   - Most prominent ocular side effect - mild blanching of the conjunctiva
   - **Not for use in cats**

3. **Agonist:** Brimonidine
4. **Antagonists**: b-blockers
   - Betaxolol
   - Timolol maleate

3. **Topical** carbonic anhydrase inhibitors (CAI)
   a) Dorzolamide
   b) Brinzolamide
   c) Dorzolamide-timolol

4. Prostaglandin analogues
   a) Latanoprost
      - Prostanoid selective FP-receptor (receptors specific for prostaglandin-F [PGF]) agonist
      - Reduces IOP by increasing aqueous humor outflow
      - May replace mannitol as a first-line drug in the emergency management of acute primary glaucoma
   b) Unoprostol

| Drug | Classification | Concentration | Indications | Cautions | Side Effects |
|---|---|---|---|---|---|
| Mannitol | Osmotic diuretic | 5–20% IV solution | Short-term use in acute 1° or 2° glaucoma | For slow IV use only, do not use in dehydrated patient or in patient with cardiac compromise | Only in patients with normal renal function |
| Glycerin | Osmotic diuretic | 50% oral solution | Short-term use in acute 1° or 2° glaucoma | Oral use only, do not use in dehydrated patient or in patient with cardiac compromise, avoid in diabetic patients | Hypotense response to glycerin variable<br>Metabolized into glucose |
| Methazolamide | Oral CAI | 25-, and 50-mg tablets | Acute and chronic 1° and 2° glaucoma | Can cause anorexia, vomiting, diarrhea, increased diuresis, malaise, and panting secondary to metabolic acidosis or hypokalemia | |
| Pilocarpine | Direct-acting cholinergic, parasympathomimetic miotic | 1%, 2%, 4%, 6%, or 8%for topical use | Acute and chronic 1° glaucoma | Avoid in patients with anterior lens luxation, uveitis, or pupillary block | |
| Carbachol | Direct-and indirect-acting cholinergic, parasympathomimetic miotic | 0.75%, 1.5%, 2.25%, or 3% for topical use | Acute and chronic 1° glaucoma | Can produce systemic toxicity; avoid in patients with cardiorespiratory disease, hyperthyroidism, or hypertension; can induce headache from ciliary spasm | |
| | | 0.01% for intracameral use | Achieving miosis during intraocular surgery (after ICLE or phacoemulsification) to reduce risk of postoperative IOP spike | For single-dose use only; can produce systemic toxicity; avoid in patients with cardiorespiratory disease, hyperthyroidism, or hypertension; can induce headache from ciliary spasm | |
| Demecarium bromide | long-acting cholinesterase (AChE) inhibitor, miotic | 0.125% or 0.25% for topical use | Chronic glaucomas amenable to miotic therapy | Use only when shorter acting miotics have proven inadequate | |
| Epinephrine | Adrenergic agonist sympathomimetic | 0.5%, 1%, and 2% for topical use | Acute and chronic 1° open-angle glaucoma | Avoid in patients with narrow-angle glaucoma, hypertensive cardiac disease, and asthma | |
| Dipivalyl epinephrine | Adrenergic agonist sympathomimetic | 0.1% for topical use | Acute and chronic 1° open-angle glaucoma | Avoid in patients with narrow-angle glaucoma, hypertensive cardiac disease, and asthma | |
| Apraclonidine | Selective $\alpha_2$-agonist | 0.5% for topical use | For use in the prevention of elevated IOP after laser procedures and cataract surgery; also effective in blunting IOP spikes occurring with cycloplegia in patients with open-angle glaucoma | Avoid in cats and in patients with cardiovascular, hepatic, and renal disease, or in patients receiving MAO inhibitors | Vomiting |
| Brimonidine | Selective $\alpha_2$-agonist | 0.2% for topical use | Acute and chronic 1° open-angle glaucoma | Avoid in cats and in patients with cardiovascular, hepatic, and renal disease, or in patients receiving MAO inhibitors | |
| Betaxolol | Selective $\beta_1$-antagonist | 0.25% or 0.5% for topical use | Acute and chronic 1° and 2° glaucoma | Caution in patients with diabetes, hyperthyroidism, or cardiac disease or severe respiratory disease | |
| Timolol maleate | Non-selective β-antagonist | 0.25% or 0.5% solution and gel-forming solution for topical use | Acute and chronic 1° and 2° glaucoma | Avoid in patients with asthma, severe obstructive pulmonary disease, or cardiac disease; caution in patients with diabetes or hyperthyroidism | |
| Dorzolamide | CAI | 2% for topical use | Acute and chronic 1° and 2° glaucoma | Avoid in patients with severe renal compromise or patients sensitive to sulfonamides | Stinging and burning<br>Can cause irreversible corneal edema in patients with corneal endothelial cell compromise |
| Brinzolamide | CAI | 1% for topical use | Acute and chronic 1° and 2° glaucoma | Avoid in patients with severe renal compromise or patients sensitive to sulfonamides | |
| Dorzolamide-timolol | CAI/nonselective β-antagonist combination | 2% dorzolamide–0.5% timolol for topical use | Acute and chronic 1° and 2° glaucoma | Refer to cautions for dorzolamide and timolol | |
| Latanoprost | Prostaglandin analogue | 0.005% for topical use | Acute and chronic 1° glaucoma | Avoid in patients with uveitis or those with severe renal or hepatic disease; induces miosis in dog, cat, and horse; avoid in patients with pupillary block glaucoma or anterior lens luxation | Intense miosis |

Questions

1. A 5yo JRT presents for anterior lens luxation with IOP of 40mmHg, which of the following drugs would be contraindicated and why?
    a) Brimonidine
    b) Timolol
    c) Dorzolamide
    d) Latanoprost

2. Which drug class is dorzolamide?
    a) Non-selective beta-antagonist
    b) CAI
    c) Selective alpha 2-agonist
    d) Prostaglandin analogue

3. Which drug class is latanoprost?
    a) Non-selective beta-antagonist
    b) CAI
    c) Selective alpha 2-agonist
    d) Prostaglandin analogue

4. Which drug class is timolol?
    a) Non-selective beta-antagonist
    b) CAI
    c) Selective alpha 2-agonist
    d) Prostaglandin analogue

Answers

A 5yo JRT presents for anterior lens luxation with IOP of 40mmHg, which of the following drugs would be contraindicated and why?
    e) Brimonidine
    f) Timolol
    g) Dorzolamide
    h) **Latanoprost – causes miosis**

Which drug classification is dorzolamide?
    i) Non-selective beta-antagonist
    **j) CAI**
    k) Selective alpha 2-agonist
    l) Prostaglandin analogue

Which drug class is latanoprost?
    m) Non-selective beta-antagonist
    n) CAI
    o) Selective alpha 2-agonist
    **p) Prostaglandin analogue**

Which drug class is timolol?
    **q) Non-selective beta-antagonist**
    r) CAI
    s) Selective alpha 2-agonist
    t) Prostaglandin analogue