

OCULAR PHARMACOLOGY – OP011

January, 2007

At the end of this session, the student will be able to:

1. List at least 5 factors affecting drug delivery to the eye and four formulations that may be used to increase drug exposure time to the eye.
2. Define glaucoma and distinguish between closed and open angle glaucoma.
3. List at least five major drug types used in glaucoma and know mechanism of action and possible side effects.
4. List two classes of drugs used as mydriatics and possible side effects.

Typical drugs to know: pilocarpine, carbachol, echothiophate, epinephrine, brimonidine, timolol, acetazolamide, brinzolamide, dorzolamide, lanaprost, isosorbide, mannitol, atropine, tropicamide, phenylephrine.

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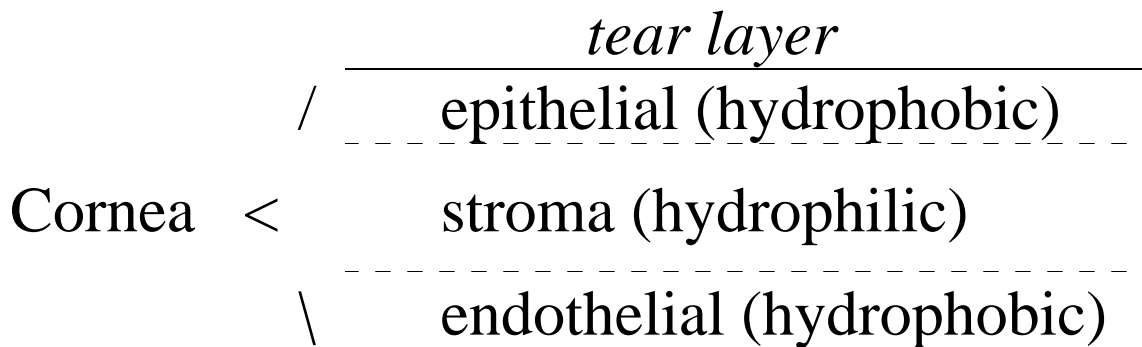
TOPICAL DRUG DELIVERY TO THE EYE

Bioavailability:

- pH, tonicity, concentration,
- lipid solubility, partition coefficient,
- vehicle, additives, compliance,
- melanin affinity.

Formulations:

- gels,
- ointments,
- solid inserts,
- soft contact lenses, collagen shields.



Remember: drugs at this site are also very accessible to the peripheral circulation.

GLAUCOMA

- increased intraocular pressure (risk factor?)
 - normally 12-20 mm Hg.
 - when to Tx – no fixed level.
 - literature sets ~21 mm Hg as upper limit of normal.
 - some safe at 30 mm Hg
 - some may have damage at 20 mm Hg.
 - General rule - if glaucomatous damage – lower pressure.

- pressure due to balance of aqueous humor:
 - **production**
 - (ciliary body).
 - **drainage.**
 - Canal of Schlemm.
 - uveoscleral outflow (up to 15%).

Closed angle glaucoma (CAG)

- ballooning of iris decreases aqueous humor flow – increases pressure.
- emergency situation.
- acute drug treatment followed by surgery.

Open angle glaucoma (OAG)

- chronic disease
- primary defect usually decreased drainage (canal of Schlemm).
- Tx: ↑ drainage and/or ↓ humor production.

DRUGS FOR GLAUCOMA

1. *Parasympathomimetics (miotics):*

- earliest used -
- **pilocarpine**, carbachol (receptor agonists).
- echothiophate (acetylcholinesterase inhibitor).

- increased outflow of aqueous humor.
 - pilocarpine for OAG and CAG.
- poor night vision, blurred vision and aching.
 - less accommodative spasm with pilocarpine.
 - brow ache clears after 2 weeks.
- contraindicated when miosis undesirable (iritis).
- avoid strong miotics in retinal detachment.

- drops (2-4x's/d); gels (1 day); inserts (7 days).

- Side effects – GI, salivation

- echothiophate – due to iris cysts and cataracts, used only when other miotics not successful.

DRUGS FOR GLAUCOMA (continued)

2. *Sympathomimetics:*

- epinephrine – better drugs now available
 - acts on α and β -adrenoceptors in ciliary body to improved outflow (uveoscleral).
 - increased outflow (yet mydriasis?) but may actually increase aqueous humor production.
 - systemic problems – avoid in hypertension and heart disease. High allergic toxic rate.
 - avoid in CAG.
 - dipivefrine – better penetration and converted to epinephrine in the eye.
- α_2 -adrenoceptor agonists - topical
 - apraclonidine - used post eye surgery
 - decreased aqueous humor production?
 - brimonidine** – most common of this class
 - decreases aqueous humor production and increases outflow (uveoscleral).
 - lowers IOP with minimal systemic effects.

DRUGS FOR GLAUCOMA (continued)

3. *β -Adrenoceptor blockers:*

- mainstay
- **timolol** (decreased MSA effect).
- useful in OAG and CAG.
- decreased aqueous humor production.
- most frequently used (no miosis or mydriasis).
- contraindications – heart failure, asthma, diabetes, heart block, sinus bradycardia.

4. *Carbonic anhydrase inhibitors:*

- acetazolamide (topical most frequent, oral or iv).
- oral not for chronic use.
- inhibits HCO_3 formation in ciliary body.
 - decreased aqueous humor production.
- iv useful for emergencies.
- side effects - metabolic acidosis, potassium depletion, fatigue, depression.
- **brinzolamide** (Azopt) and **dorzolamide** (Trusopt) are topical agents used commonly.

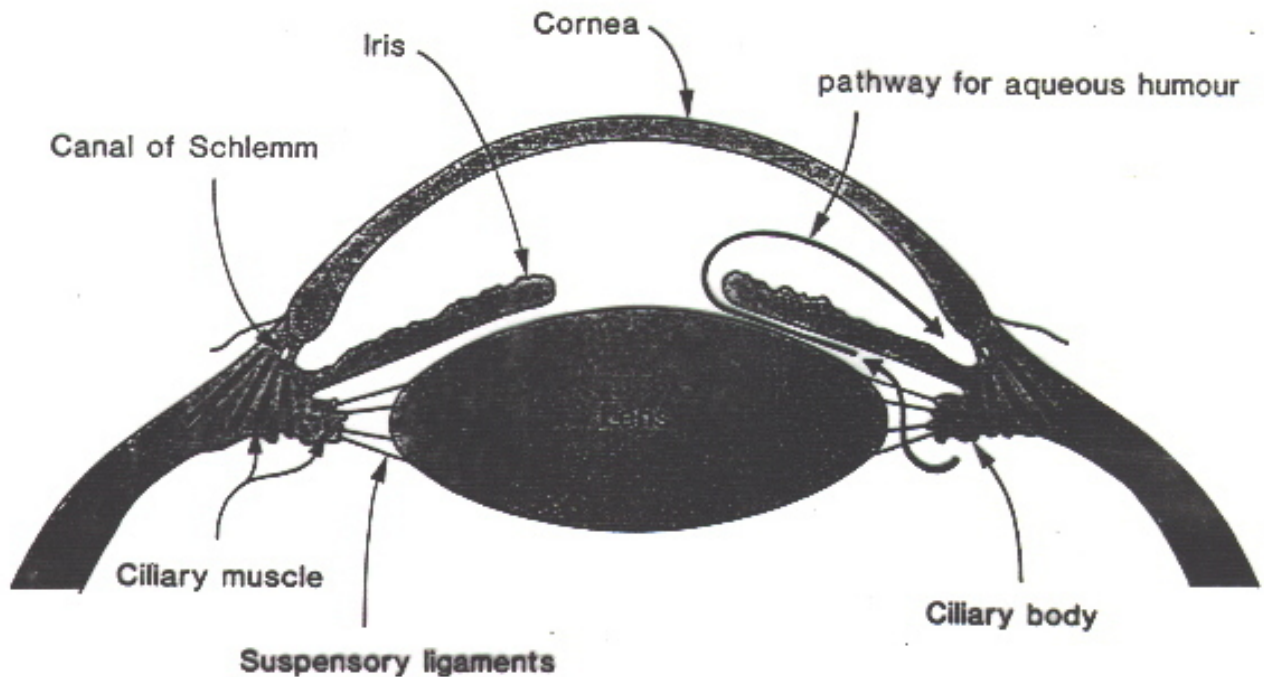
DRUGS FOR GLAUCOMA (continued)

5. *Prostaglandin Analogue*s

- novel class of drugs for glaucoma
- prostaglandins decrease IOP by increasing uveoscleral outflow.
 - in humans < 15% of aqueous humor drained by this route.
 - ciliary muscle contraction (pilocarpine) decreases outflow and relaxation (atropine) increases outflow.
 - increase outflow by both the relaxing ciliary muscle and directly altering extracellular matrix to decrease outflow resistance.
- **latanoprost** is a topically applied prostaglandin $F_{2\alpha}$ analogue.
 - may increase/change iris pigmentation (brown), produce eyelid darkening and growth of eyelashes. May be permanent.

6. *Hypertonic solutions:*

- **isosorbide** (oral), **mannitol** (iv).
- emergency management of angle closure.
- may be used to decrease pressure pre-operatively.
- avoid in severe dehydration, anuria, pulmonary edema.



SUMMARY

	<u>pupil</u>	<u>outflow</u>	<u>AH</u>
parasympathomometric	<i>miosis</i>	↑	-
Sympathomimetic			
epinephrine	<i>mydriasis?</i>	↑	↑?
α ₂ agonist	<i>neutral</i>	↑	↓
β-blocker	<i>neutral</i>	-	↓
CA inhibitor	<i>neutral</i>	-	↓
PG analogue	<i>neutral</i>	↑	-

Treatment

1. β -blocker – mainstay

- if contraindicated or ineffective

2. try monotherapy with

- prostaglandins
- local CAI's
- α_2 adrenergic agonists
- if monotherapy ineffective

3. try combinations

- β -blocker + (prostaglandin or topical CAI's)
- prostaglandin + (β -blocker or topical adrenergic agent or CAI's)

4. parasympathomimetics

- newer drugs better
- third line drugs due to side effects
- may use as miotic with prostaglandin or β -blocker

CYCLOPLEGIC AND MYDRIATIC AGENTS

Mydriatic - useful for examination of the eye.

Cycloplegic - useful for accurate refractions and providing relief from ciliary spasm during inflammation.

Parasympathoplegic Drugs:

- **atropine** (7-10 days); **tropicamide** (~1-6 hours).
- produce both mydriasis and cycloplegia.
- note duration of action.
- contraindicated in glaucoma.
- avoid in young children and infants (very sensitive to CNS effects).

Sympathomimetic Drugs

- **phenylephrine** (3-7 h).
- mydriatic with little/no cycloplegia.
- use with caution in glaucoma (short $t_{1/2}$), heart disease and hypertension.