

OCULAR PHARMACOLOGY AND TOXICOLOGY

General Pharmacological Principles:

The study of ocular pharmacology begins with a review of some general principles of pharmacology, with particular attention to special features of eye.

Pharmacodynamics:

It is the biological and therapeutic effect of the drug ([mechanism of action](#))

Most drugs act by binding to regulatory macromolecules, usually neurotransmitters or hormone receptors or enzymes

If the drug is working at the receptor level, it can be [agonist or antagonist](#)

If the drug is working at the enzyme level, it can be [activator or inhibitor](#)

:Pharmacokinetics

To achieve a therapeutic effect, a drug must reach its site of action in sufficient concentration.

It is the absorption, distribution, metabolism, and excretion of the drug

The concentration at site of action is a function of the following:

- Amount administered
- Extent and rate of absorption at administration site
- Distribution and binding in tissues
- Movement by bulk flow in circulating fluids
- Transport between compartments
- Biotransformation
- Excretions

A drug can be delivered to ocular tissue as:

| <u>Local</u> | <u>systemic</u> |
|-----------------------|-----------------|
| Eye drop | Orally |
| Ointment | IV |
| Periocular injection | |
| Intraocular injection | |

Factors Influencing Local Drug Penetration into Ocular Tissue

| | |
|-----------------------------------|--|
| Drug concentration and solubility | the higher the concentration the better the penetration e.g pilocarpine 1-4% but <u>limited by</u> reflex tearing |
| Viscosity | addition of methylcellulose and polyvinyl alcohol increases drug penetration by <u>increasing the contact time</u> with the cornea and <u>altering corneal epithelium</u> |
| Lipid solubility | because of the lipid rich environment of the epithelial cell membranes, <u>the higher lipid solubility the more the penetration.</u> Conj. Permeability to water soluble x20 > cornea. |
| Surfactants | the preservatives used in ocular preparations <u>alter cell membrane in the cornea</u> and increase drug permeability e.g. benzylkonium and thiomersal |
| pH | the normal tear pH is 7.4 and if the drug pH is much different, this will cause reflex tearing |
| Drug tonicity | when an alkaloid drug is put in relatively alkaloid medium, the proportion of the uncharged form will increase, thus more penetration |

Local Drug

| | |
|--------------------------------------|--|
| <p>Eye drops</p> | <p>Eye drops- most common one drop = 50 µl volume of conjunctival cul-de-sac 7-10 µl 20% of administered drug is retained Rapid turnover of tear occurs, 16% per minute in undistributed eye. 50% remains after 4 minutes & only 17% after 10 minutes of the drug that reached the tear reservoir. Measures to increase drop absorption: -wait 5-10 minutes between drops -compress lacrimal sac -keep lids closed for 5 minutes after instillation</p> |
| <p>Ointments</p> | <p>Increase the contact time of ocular medication to ocular surface thus better effect It has the disadvantage of <u>vision blurring</u> The drug has to be high lipid soluble with some water solubility to have the maximum effect as ointment</p> |
| <p>Peri-ocular injections</p> | <p>They reach behind iris-lens diaphragm better than topical application E.g. subconjunctival, subtenon, peribulbar, or retrobulbar This route bypass the conjunctival and corneal epithelium which is good for drugs with low lipid solubility (e.g. penicillin) Also steroid and local anesthetics can be applied this way</p> |
| <p>Intraocular injections</p> | <p><u>Intracameral</u> acetylcholine (miochol) during cataract surgery <u>Intravitreal</u> antibiotics in cases of endophthalmitis <u>Intravitreal</u> steroid in macular edema <u>Intravitreal</u> Anti-VEGF for DR</p> |

Sustained-release devices

These are devices that deliver an adequate supply of medication at a steady-state level

E.g:

- 1-Ocusert delivering pilocarpine
- 2-Timoptic XE delivering timolol
- 3-Ganciclovir sustained-release intraocular device
- 4-Collagen shields

Systemic drugs : oral and IV

| | |
|------------------------------|---|
| lipid solubility of the drug | more penetration with high lipid solubility |
| Protein binding | more effect with low protein binding |
| Eye inflammation | more penetration with ocular inflammation |

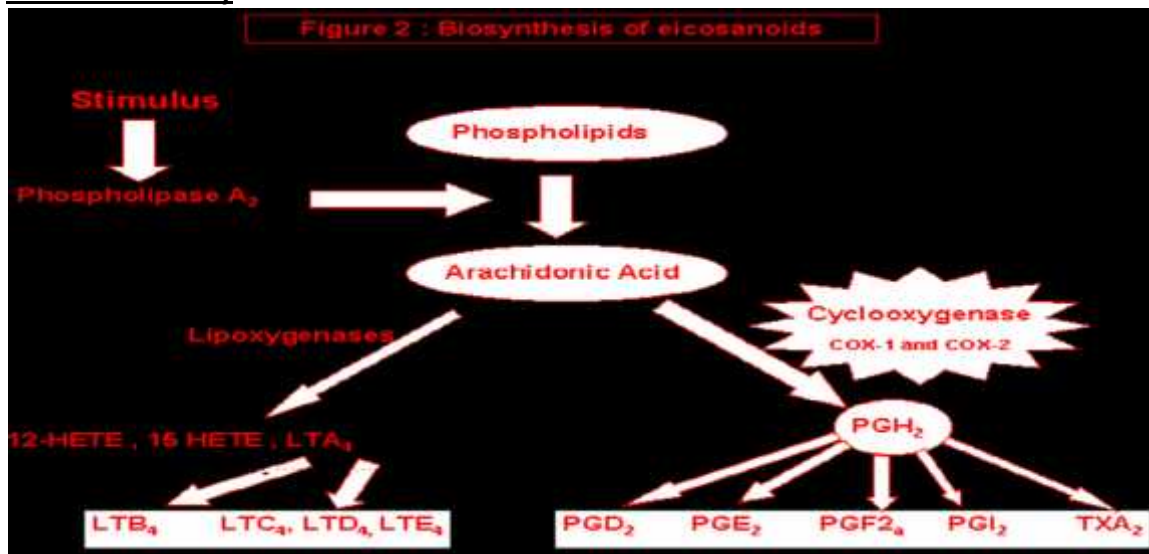
Ocular Pharmacotherapeutics:

| | E.g. | Uses | Mechanisms: | Side effects: |
|--|---|---|--|--|
| <p>Cholinergic agonists</p> <ul style="list-style-type: none"> ▪ 1-Directly acting agonists: <ul style="list-style-type: none"> ▪ 2- Indirectly acting (anti-cholinesterases) : More potent with longer duration of action ▪ a- Reversible inhibitors <p>b-Irreversible:</p> | <p>pilocarpine, acetylcholine (miochol), carbachol (miostat)</p> <p>physostigmine</p> <p>phospholine iodide</p> | <p>miosis, glaucoma</p> <p>Use in glaucoma and lice infestation</p> <p>in accommodative esotropic</p> | <p>-Miosis by contraction of the iris sphincter muscle -increases aqueous outflow through the trabecular meshwork by longitudinal ciliary muscle contraction -Accommodation by circular ciliary muscle contraction</p> | <p>-<u>Local</u>: diminished vision (<u>myopia</u>), <u>headache</u>, cataract, miotic cysts, and rarely retinal detachment -<u>systemic side effects</u>: lacrimation, salivation, perspiration, bronchial spasm, urinary urgency, nausea, vomiting, and diarrhea</p> <p>-can cause CNS side effects</p> <p>-iris cyst and anterior subcapsular cataract C/I in angle closure glaucoma, asthma, Parkinsonism causes apnea if used with succinylcholine or procaine</p> |
| <p>Cholinergic antagonists</p> | <p>tropicamide, cyclopentolate, homatropine, scopolamine, atropine</p> | <p>fundoscopy, cycloplegic refraction, anterior uveitis</p> | <ul style="list-style-type: none"> ▪ Cause :mydriasis (by paralyzing the sphincter muscle) with cycloplegia (by paralyzing the ciliary muscle) | <p>local: allergic reaction, blurred vision Systemic: nausea, vomiting, pallor, vasomotor collapse, constipation, urinary retention, and confusion specially in children they might cause flushing, fever, tachycardia, or</p> |

| | | | | |
|---|--|--|--|---|
| | | | | delerium Treatment by DC or physostigmine |
| <p>Adrenergic agonists</p> <p>1-Non-selective agonists ($\alpha_1, \alpha_2, \beta_1, \beta_2$)</p> <p>▪ 2-Alpha-1 agonists</p> <p>▪ 2-Alpha-2 agonists</p> | <p>-epinephrine, -depevefrin (pro-drug of epinephrine)</p> <p>phenylepherine</p> <p>brimonidine, apraclonidine</p> | <p>Glaucoma</p> <p>mydriasis (<u>without</u> cycloplegia), decongestant</p> <p>glaucoma treatment, prophylaxis against IOP spiking after glaucoma laser procedures</p> | <p>decrease aqueous production, and increase uveoscleral outflow</p> | <p><u>Side effects:</u> headache, arrhythmia, increased blood pressure, conjunctival adrenochrome, cystoid macular edema in aphakic eyes <u>C/I</u> in closed angle glaucoma</p> <p>-Can cause significant <u>increase in blood pressure</u> specially in infant and susceptible adults</p> <p>-Rebound congestion</p> <p>-precipitation of acute angle-closure glaucoma in patients with narrow angles</p> <p><u>local:</u> allergic reaction, mydriasis, lid retraction, conjunctival blanching</p> <p><u>systemic:</u> oral dryness, headache, fatigue, drowsiness, orthostatic hypotension, vasovagal attacks</p> <p><u>Contraindications:</u> infants, MAO inhibitors users</p> |
| <p>Alpha Adrenergic Antagonists</p> <p>1-Beta-adrenergic blockers</p> | <p>thymoxamine, dapiprazole</p> <p>non-selective: timolol, levobunolol, metipranolol, carteolol</p> | <p>-to reverse pupil dilation produced by phenylepherine</p> <p>-Not widely used</p> <p>glaucoma</p> | <p>reduce the formation of aqueous humor by the ciliary</p> | <p>▪ <u>bronchospasm</u> (less with betaxolol),</p> |

| | | | | |
|--|--|---|--------------------------------------|--|
| | selective: betaxolol (beta 1 "cardioselective") | | body | cardiac impairment |
| Carbonic Anhydrase Inhibitors | acetazolamide, methazolamide, dichlorphenamide, dorzolamide, brinzolamide. | glaucoma, cystoid macular edema, pseudotumour cerebri | aqueous suppression | myopia, parasthesia, anorexia, GI upset, headache, altered taste and smell, Na and K depletion, metabolic acidosis, renal stone, bone marrow suppression "aplastic anemia" -Contraindication: sulpha allergy, digitalis users, pregnancy |
| Osmotic agents: Dehydrate vitreous body which reduce IOP significantly | Glycerol 50% syrup (cause nausea, hyperglycemia) ▪ Mannitol 20% IV (cause fluid overload and not used in heart failure) | | | |
| Prostaglandin Analogues | latanoprost, bimatoprost, travoprost, unoprostone | glaucoma | increase uveoscleral aqueous outflow | darkening of the iris (<u>heterochromia iridis</u>), lengthening and thickening of eyelashes, intraocular inflammation, macular edema |

Anti-inflammatory



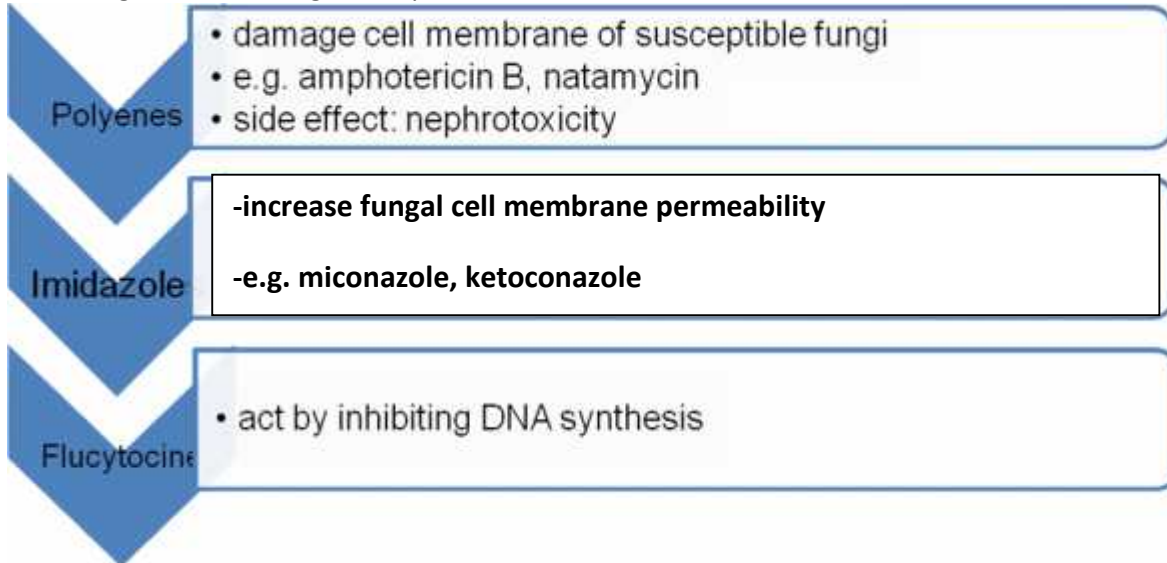
| | | | | |
|--------------------------|--|--|--|--|
| Anti-inflammatory | | | | |
| 1- Corticosteroids | | | | |

| | | |
|---------------------------|---|---|
| <p>Antibiotics</p> | <p>Penicillins Cephalosporins Sulfonamides Tetracyclines Chloramphenicol Aminoglycosides Fluoroquinolones Vancomycin Macrolides</p> | <p>-Used topically in prophylaxis (pre and postoperatively) and treatment of ocular bacterial infections.</p> <p>Used orally for the treatment of preseptal -cellulitis</p> <p>e.g. amoxicillin with clavulonate, cefaclor</p> <p>Used intravenously for the treatment of orbital -cellulitis</p> <p>e.g. gentamicin, cephalosporin, vancomycin, flagyl</p> <p>-Can be injected intravitally for the treatment of endophthalmitis</p> |
|---------------------------|---|---|

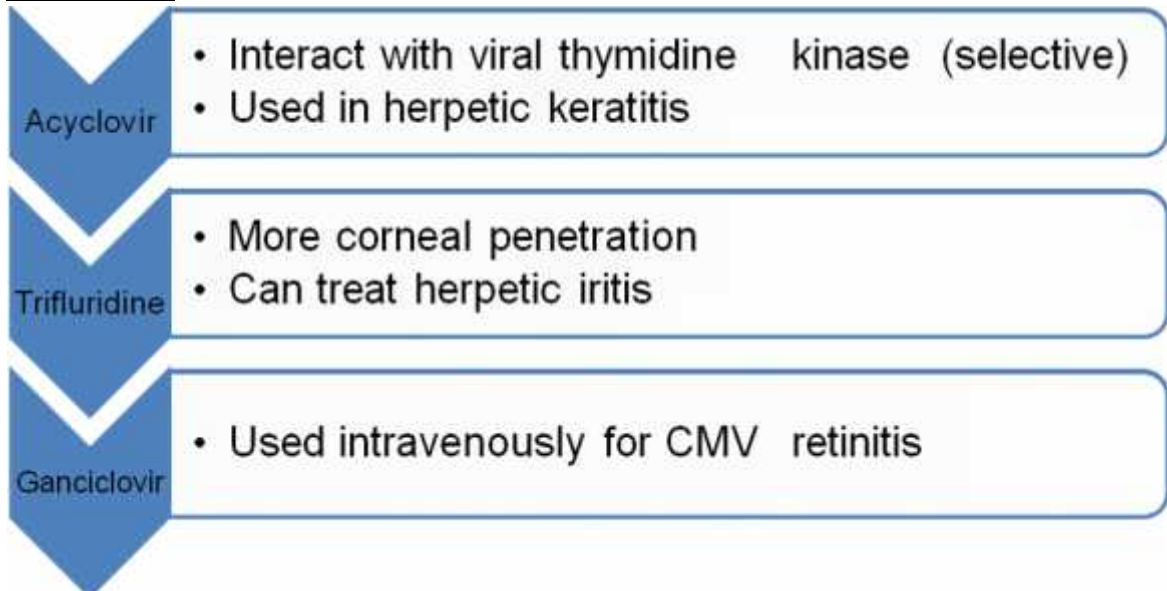
- Trachoma can be treated by topical and systemic tetracycline or erythromycin, or systemic azithromycin.
- Bacterial keratitis (bacterial corneal ulcers) can be treated by topical fortified penicillins, cephalosporins, aminoglycosides, vancomycin, or fluoroquinolones.
- Bacterial conjunctivitis is usually self limited but topical erythromycin, aminoglycosides, fluoroquinolones, or chloramphenicol can be used

Antifungals

Uses: fungal keratitis, fungal endophthalmitis



Antivirals



Ocular diagnostic drugs

Fluorescein dye

Available as drops or strips

Uses: stain corneal abrasions, applanation tonometry, detecting wound leak, NLD obstruction, fluorescein angiography

Caution:

stains soft contact lens

drops can be contaminated by Pseudomonas sp

-
- **Rose bengal stain**
- Stains devitalized epithelium
- Uses: severe dry eye, herpetic keratitis

Local Anesthetics

| | |
|---|---|
| Topical | Orbital infiltration |
| E.g. propacaine, tetracaine <u>Uses:</u> applanation tonometry, gonioscopy, removal of corneal foreign bodies, removal of sutures, examination of patients who cannot open eyes because of pain <u>Adverse effects:</u> toxic to corneal epithelium, allergic reaction rarely | peribulbar or retrobulbar cause anesthesia and akinesia for intraocular surgery e.g. lidocaine, bupivacaine |

Other Ocular Preparations

Lubricants

drops or ointments

Polyvinyl alcohol, cellulose, methylcellulose

Preserved or preservative free (free is better)

Ocular Toxicology

Complications of Topical Administration

| | |
|-------------------|--|
| Mechanical injury | from the bottle e.g. corneal abrasion |
| Pigmentation | epinephrine-adrenochrome |
| Ocular damage | e.g. topical anesthetics, benzylkonium |
| Hypersensitivity | e.g. atropine, neomycin, gentamicin |
| Systemic effect | topical phenylephrine can increase BP |

| | |
|----------------------|--|
| Amiodarone | A cardiac arrhythmia drug- -Causes optic neuropathy (mild decreased vision, visual field defects, bilateral optic disc swelling) -Also causes corneal vortex keratopathy (corneal verticillata) which is whorl-shaped pigmented deposits in the corneal epithelium |
| Digitalis | -A cardiac failure drug -Causes chromatopsia (objects appear yellow) with overdose |
| Chloroquines | -E.g. chloroquine, hydroxychloroquine -Used in malaria, rheumatoid arthritis, SLE -Cause vortex keratopathy (corneal verticillata) which is usually asymptomatic but can present with glare and photophobia -Also cause retinopathy (bull's eye maculopathy) |
| Chorpromazine | A psychiatric drug- -Causes corneal punctate epithelial opacities, lens surface opacities Rarely symptomatic- Reversible with drug discontinuation- |

| | |
|--------------------------|---|
| Thioridazine | -A psychiatric drug -Causes a pigmentary retinopathy after high dosage |
| Diphenylhydantoin | <ul style="list-style-type: none"> ▪ An epilepsy drug ▪ Causes dosage-related cerebellar-vestibular effects: <ul style="list-style-type: none"> ▪ Horizontal nystagmus in lateral gaze ▪ Diplopia, ophthalmoplegia ▪ Vertigo, ataxia ▪ Reversible with the discontinuation of the drug |
| Topiramate | -A drug for epilepsy -Causes acute angle-closure glaucoma (acute eye pain, redness, blurred vision, haloes). -Treatment of this type of acute angle-closure glaucoma is by cycloplegia and topical steroids (rather than iridectomy) with the discontinuation of the drug |
| Ethambutol | -An anti-TB drug -Causes a dose-related optic neuropathy -Usually reversible but occasionally permanent visual damage might occur |

Agents That Can Cause Toxic Optic Neuropathy

Methanol -Ethylene glycol (antifreeze) -Chloramphenicol -Isoniazid -Ethambutol -Digitalis
 Chloroquine -Streptomycin -Amiodarone -Quinine
 Vincristine and methotrexate (chemotherapy medicines)
 Sulfonamides -Melatonin with Zoloft (sertraline, Pfizer)
 High-protein diet -Carbon monoxide -Lead -Mercury
 Thallium (alopecia, skin rash, severe vision loss)
 Malnutrition with vitamin B-1 deficiency
 Pernicious anemia (vitamin B-12 malabsorption)
 Phenomenon -Radiation (unshielded exposure to >3,000 rads)

HMG-CoA reductase inhibitors (statins)

- Cholesterol lowering agents
- E.g. pravastatin, lovastatin, simvastatin, fluvastatin, atorvastatin, rosuvastatin
- Can cause cataract in high dosages specially if used with erythromycin

Other agents

| | |
|----------------------------------|--|
| methanol | optic atrophy and blindness |
| Contraceptive pills | pseudotumor cerebri (papilledema), and dryness (CL intolerance) |
| Chloramphenicol and streptomycin | optic atrophy |
| Hypervitaminosis A | yellow skin and conjunctiva, pseudotumor cerebri (papilledema), retinal hemorrhage |
| Hypovitaminosis A | night blindness (nyctalopia), keratomalacia |

Please pray for me

**GOOD LUCK
 DONE BY: RAHMAH ALARIYANI**