Ocular pharmacology and toxicology

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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.

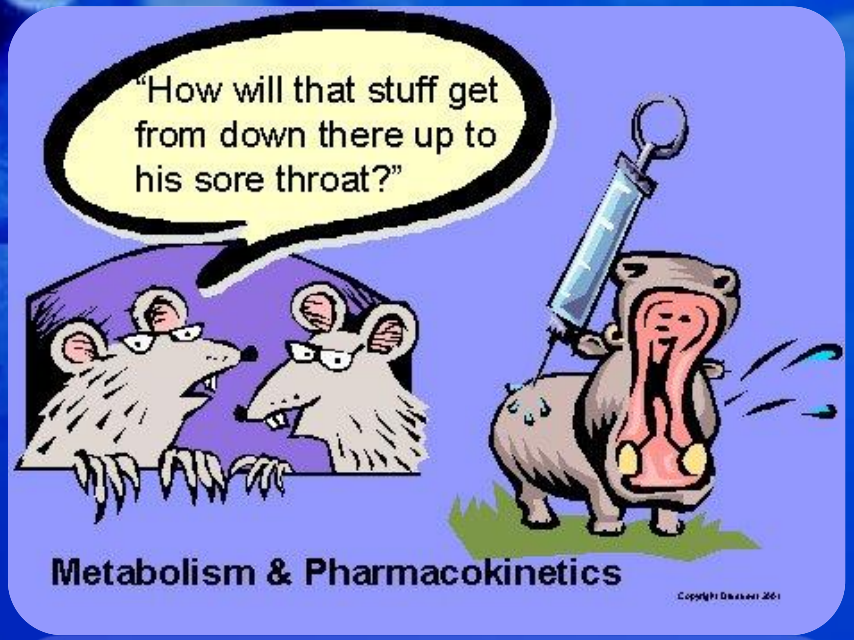
Pharmaco-dynamics

- 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

Pharmaco-kinetics

- 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
- Transport between compartments
- Biotransformation
- Excretions

- A drug can be delivered to ocular tissue as:

Locally:

Eye drop

Ointment

Periocular injection

Intraocular injection

Systemically:

Orally

IV

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 limited by reflex tearing
- **Viscosity:** addition of methylcellulose and polyvinyl alcohol increases drug penetration by increasing the contact time with the cornea and altering corneal epithelium
- **Lipid solubility:** because of the lipid rich environment of the epithelial cell membranes, the higher lipid solubility the more the penetration.

Factors Influencing Local Drug Penetration into Ocular Tissue

- **Surfactants:** the preservatives used in ocular preparations alter cell membrane in the cornea 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

Eye drops

- Eye drops- most common
- one drop = 50 µl
- volume of conjunctival cul-de-sac = 10 µl
- **20% of administrated drug is retained**
- Rapid turnover of tears occurs:
  - 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

Ointments

- **Increase the contact time** of ocular medication to ocular surface thus better effect
- It has the disadvantage of **vision blurring**
- The drug has to be high lipid soluble with some water solubility to have the maximum effect as ointment

Peri-ocular injections

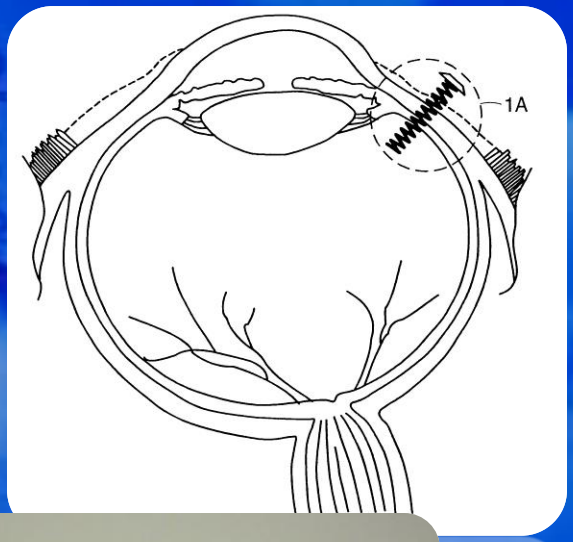
- They reach behind iris-lens diaphragm better than topical application
- E.g. subconjunctival, subtenon, peribulbar, or retrobulbar
- This route bypass the conjunctival and corneal epithelium which is good for drugs with low lipid solubility (e.g. penicillin)
- Also steroid and local anesthetics can be applied this way

Intraocular injections

- **Intracameral or intravitreal:**
  - Intracameral acetylcholine (miochol) during cataract surgery
  - Intravitreal antibiotics in cases of endophthalmitis
  - Intravitreal steroids in macular edema
  - Intravitreal Anti-VEGF for DR

Sustained-release devices

- These are devices that deliver an adequate supply of medication at a steady-state level
- E.g.
  - Ozerdex sustained release dexamethasone
  - Timoptic XE delivering timolol
  - Ganciclovir sustained-release intraocular device
  - Collagen shields



Systemic drugs

- Oral or IV
- Factor influencing systemic drug penetration into ocular tissue:
  - **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 Pharmaco-therapeutics

Cholinergic agonists

- Directly acting agonists:
  - E.g. pilocarpine, acetylcholine (miochol), carbachol (miostat)
  - Uses: **miosis, glaucoma**
  - Mechanisms:
    - 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
  - Side effects:
    - Local: diminished vision (myopia), headache, cataract, miotic cysts, and rarely retinal detachment
    - systemic side effects: lacrimation, salivation, perspiration, bronchial spasm, urinary urgency, nausea, vomiting, and diarrhea

Cholinergic agonists

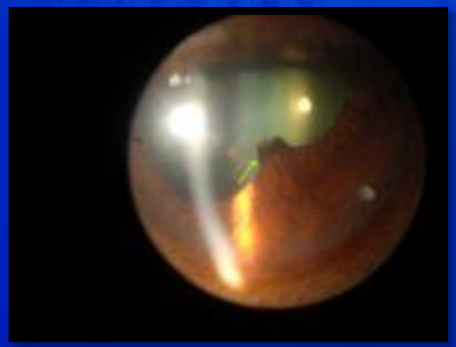
- Indirectly acting (anti-cholinesterases) :
  - More potent with longer duration of action
  - Reversible inhibitors
    - e.g. **physostigmine**
    - used in glaucoma and lice infestation of lashes
    - can cause CNS side effects

Cholinergic agonists

- Indirectly acting (anticholinesterases):
  - Irreversible:
    - e.g. **phospholine iodide**
    - Uses: in accommodative esotropia
    - side effects: iris cyst and anterior subcapsular cataract
    - C/I in angle closure glaucoma, asthma, Parkinsonism
    - causes apnea if used with succinylcholine or procaine

Cholinergic antagonists

- E.g. tropicamide, cyclopentolate, homatropine, scopolamine, atropine
- Cause **mydriasis** (by paralyzing the sphincter muscle) with **cycloplegia** (by paralyzing the ciliary muscle)
- Uses: fundoscopy, cycloplegic refraction, anterior uveitis
- Side effects:
  - 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 delerium
  - Treatment by DC or physostigmine



Adrenergic agonists

- Non-selective agonists (α_1, α_2, β_1, β_2)
  - E.g. epinephrine, depevefrin (pro-drug of epinephrine)
  - Uses: glaucoma
  - Side effects: headache, arrhythmia, increased blood pressure, conjunctival adrenochrome, cystoid macular edema in aphakic eyes
  - C/I in closed angle glaucoma

Adrenergic Agonists

- Alpha-1 agonists
- E.g. **phenylepherine**
- Uses: **mydriasis (without cycloplegia), decongestant**
- Adverse effect:
  - Can cause significant increase in blood pressure specially in infant and susceptible adults
  - Rebound congestion
  - precipitation of acute angle-closure glaucoma in patients with narrow angles

Adrenergic agonists

- Alpha-2 agonists
  - E.g. **brimonidine, apraclonidine**
  - Uses: glaucoma treatment, prophylaxis against IOP spiking after glaucoma laser procedures
  - Mechanism: decrease aqueous production, and increase uveoscleral outflow
  - Side effects:
    - local: allergic reaction, mydriasis, lid retraction, conjunctival blanching
    - systemic: oral dryness, headache, fatigue, drowsiness, orthostatic hypotension, vasovagal attacks
  - Contraindications: **infants, MAO inhibitors users**

Beta-adrenergic blockers

- E.g.
  - non-selective: timolol, levobunolol
  - selective: betaxolol (beta 1 “cardioselective”)
- Uses: glaucoma
- Mechanism: reduce the formation of aqueous humor by the ciliary body
- Side effects: **bronchospasm** (less with betaxolol), cardiac impairment

Carbonic Anhydrase Inhibitors

- E.g. acetazolamide, methazolamide, dorzolamide, brinzolamide.
- Uses: **glaucoma, cystoid macular edema, pseudo-tumour cerebri**
- Mechanism: aqueous suppression
- Side effects: 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
- E.G.
  - Glycerol 50% syrup (cause nausea, hyperglycemia)
  - Mannitol 20% IV (cause fluid overload and not used in heart failure)

Prostaglandin Analogues

- E.g. latanoprost, bimatoprost, travoprost
- Uses: glaucoma
- Mechanism: increase uveoscleral aqueous outflow
- Side effects: darkening of the iris (heterochromia iridis), lengthening and thickening of eyelashes, intraocular inflammation, macular edema

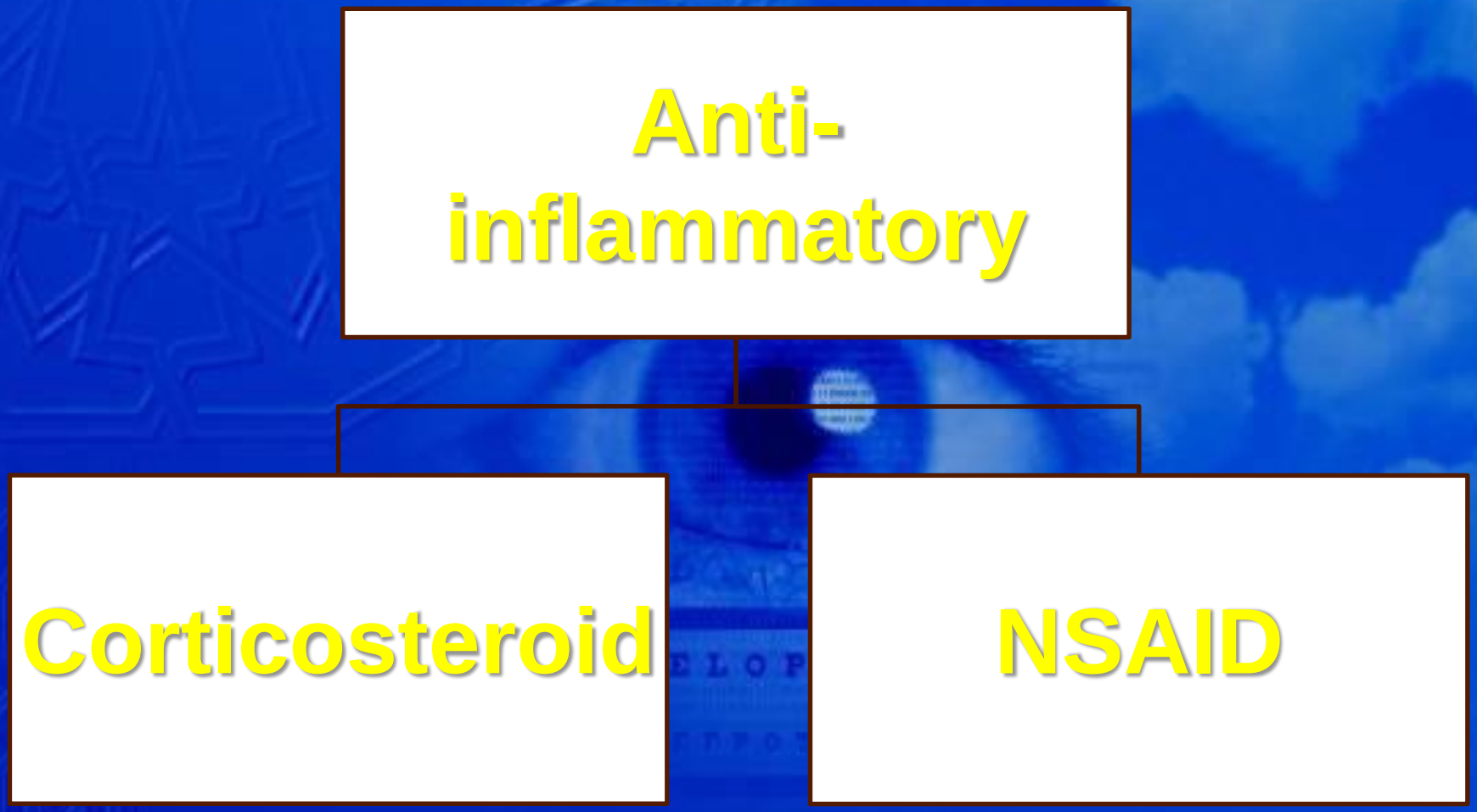
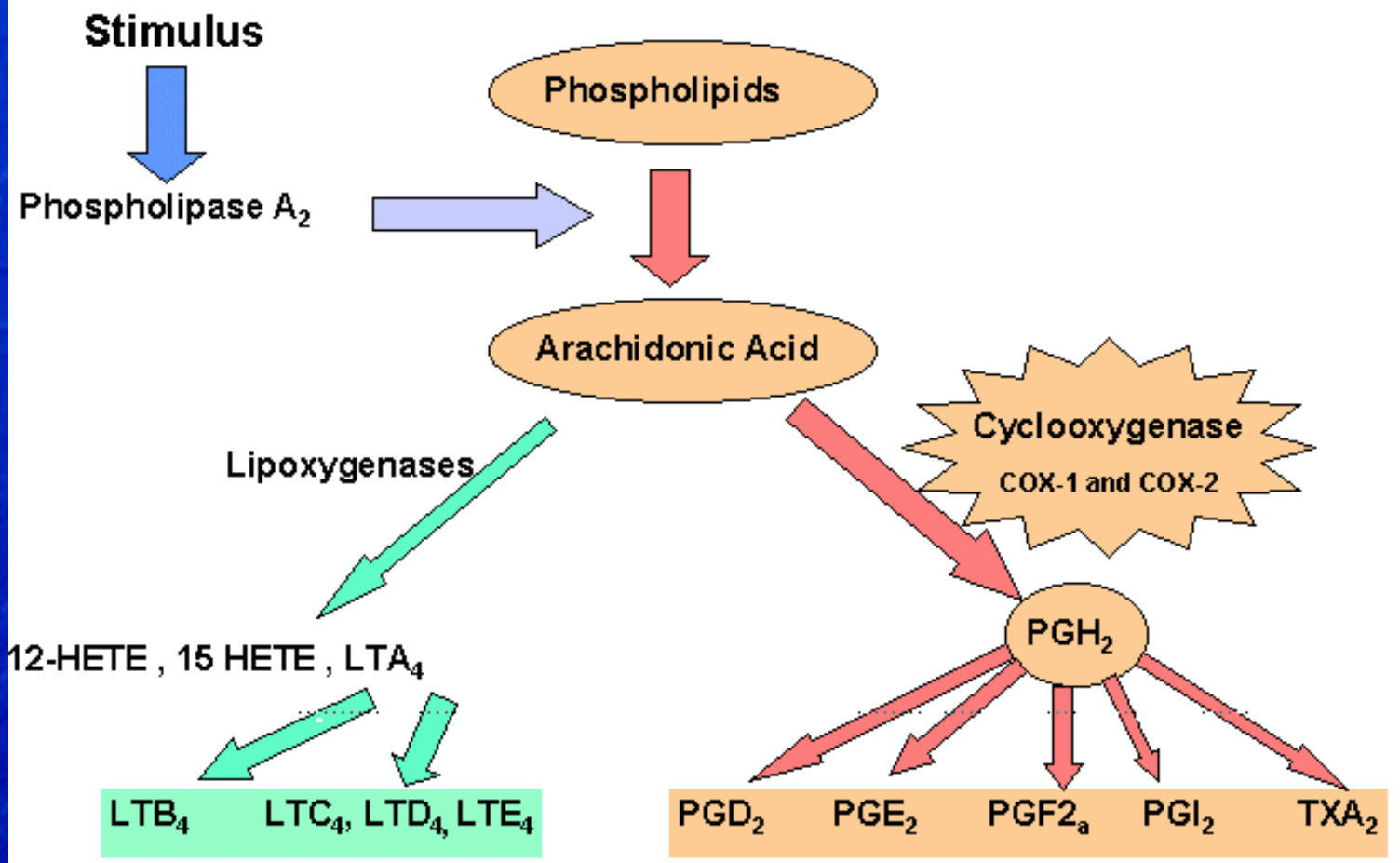

Anti-inflammatory
Corticosteroid
NSAID

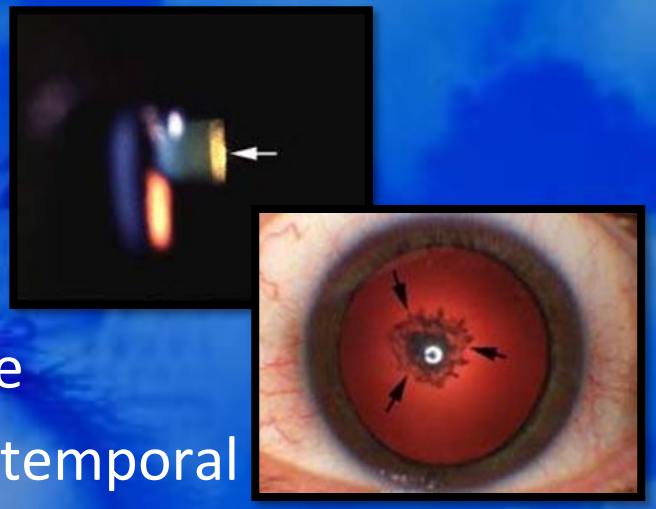
Figure 2 : Biosynthesis of eicosanoids



Corticosteroids

- Topical
  - E.g. fluorometholone, prednisolone, dexamethasone, hydrocortisone
  - Mechanism: inhibition of arachidonic acid release from phospholipids by **inhibiting phospholipase A2**
  - Uses: postoperatively, anterior uveitis, severe allergic conjunctivitis, vernal keratoconjunctivitis, prevention and suppression of corneal graft rejection, episcleritis, scleritis
  - Side effects: susceptibility to infections, glaucoma, cataract, scleral melting, skin atrophy

Corticosteroids



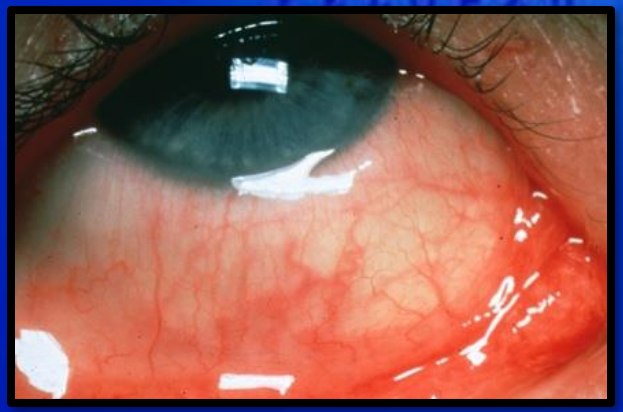
- Systemic:
  - E.g. prednisolone, methylprednisolone
  - Uses: posterior uveitis, optic neuritis, temporal arteritis with anterior ischemic optic neuropathy
  - Side effects:
    - **Local:** posterior subcapsular cataract, glaucoma, central serous retinopathy
    - **Systemic:** suppression of pituitary-adrenal axis, hyperglycemia, osteoporosis, peptic ulcer, psychosis

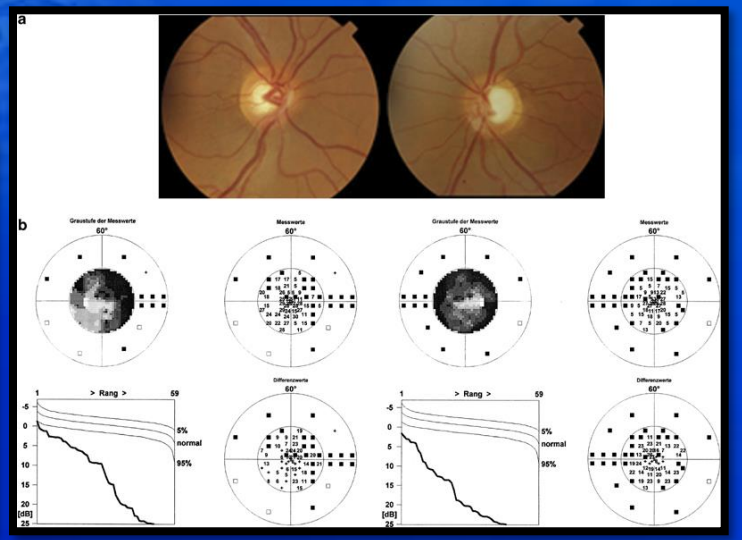
NSAIDs

- E.g. ketorolac, diclofenac, nepafenac
- Mechanism: inactivation of **cyclo-oxygenase**
- Uses: post-operatively, episcleritis/scleritis, mild uveitis, cystoid macular edema, preoperatively to prevent miosis during surgery
- Side effects: stinging and burning. Rarely: corneal erosion or melting

Anti-allergy

- Avoidance of allergens, cold compress, lubrications
- Antihistamines (e.g.pheniramine, levocabastine)
- Decongestants (e.g. naphazoline, phenylepherine, tetrahydrozaline)
- Mast cell stabilizers (e.g. cromolyn, nedocromil, olopatadine)
- NSAID (e.g. ketorolac)
- Steroids (e.g. fluorometholone, prednisolone)
- Drug combinations





Antibiotics

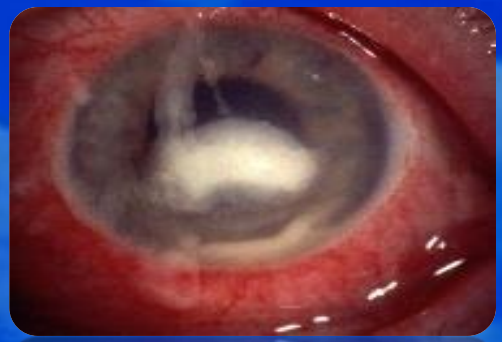
- Penicillins
- Cephalosporins
- Sulfonamides
- Tetracyclines
- Chloramphenicol
- Aminoglycosides
- Fluoroquinolones
- Vancomycin
- Macrolides

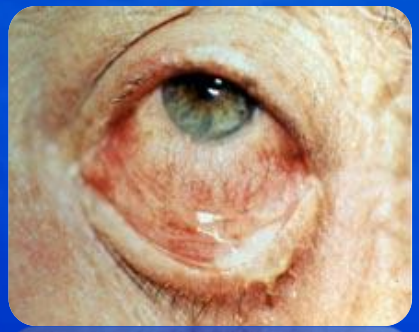
Antibiotics

- Used topically in prophylaxis (pre and postoperatively) and treatment of ocular bacterial infections.
- Used orally for the treatment of preseptal cellulitis
  - e.g. amoxycillin with clavulonate, cefaclor
- Used intravenously for the treatment of orbital cellulitis
  - e.g. gentamicin, cephalosporin, vancomycin, flagyl
- Can be injected intravitrally for the treatment of endophthalmitis

Antibiotics

- 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
- Polyenes
  - damage cell membrane of susceptible fungi
  - e.g. amphotericin B, natamycin
  - side effect: nephrotoxicity
- Imidazoles
  - increase fungal cell membrane permeability
  - e.g. miconazole, ketoconazole
- Flucytocine
  - act by inhibiting DNA synthesis

Antivirals

- **Acyclovir**

Interact with viral thymidine kinase (selective)

Used in herpetic keratitis

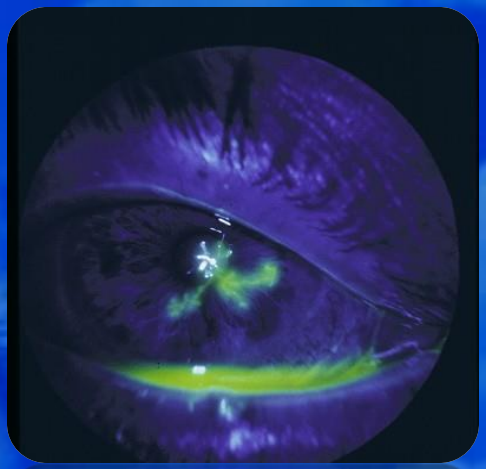
- **Trifluridine**

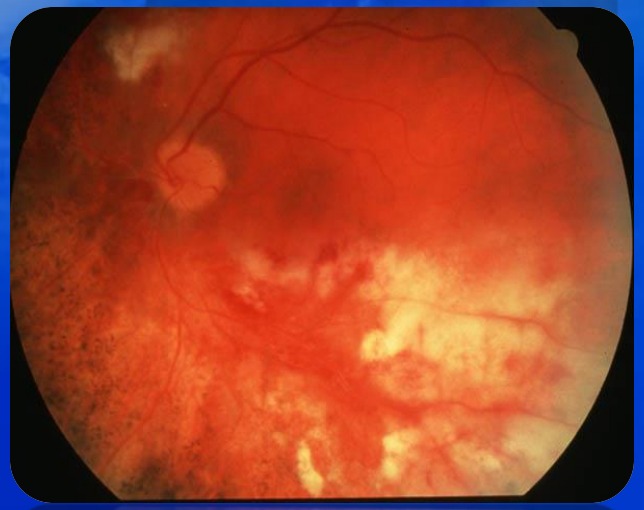
More corneal penetration

Can treat herpetic iritis

- **Ganciclovir**

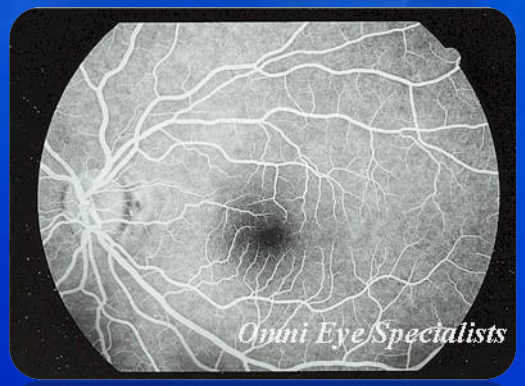
Used intravenously for CMV retinitis





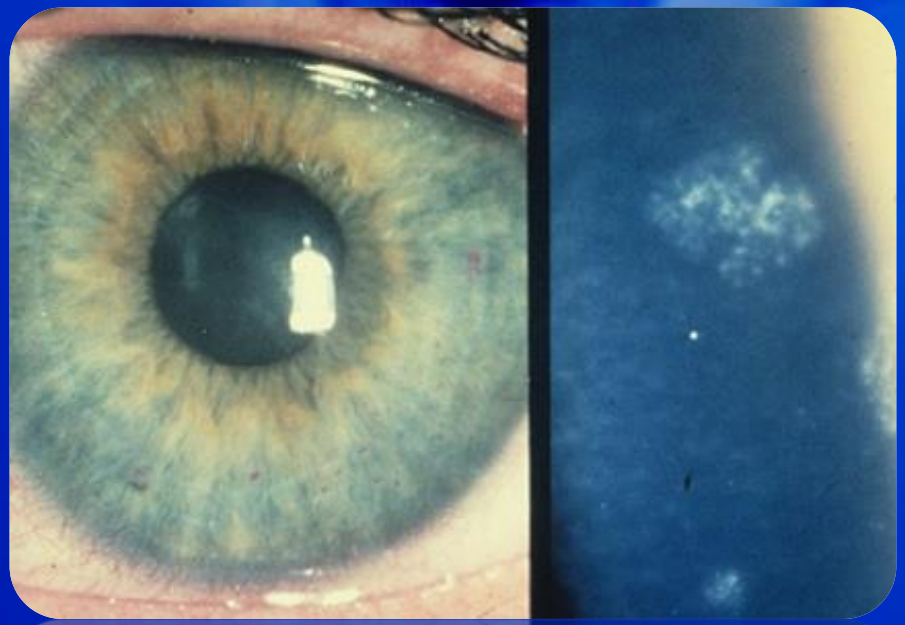
Ocular diagnostic drugs

- **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
    - Fluorescein drops can be contaminated by Pseudomonas sp.



Ocular diagnostic drugs

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

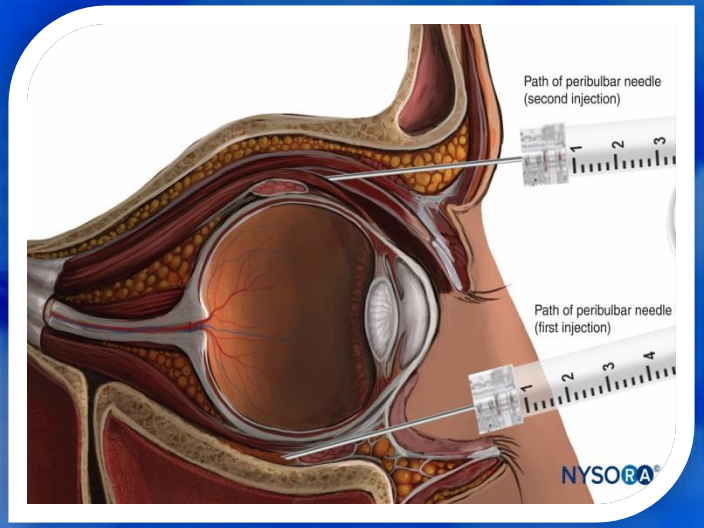


Local Anesthetics

- Topical
  - E.g. propacaine, tetracaine
  - Uses: applanation tonometry, goniscopy, removal of corneal foreign bodies, removal of sutures, examination of patients who cannot open eyes because of pain
  - Adverse effects: toxic to corneal epithelium, allergic reaction rarely

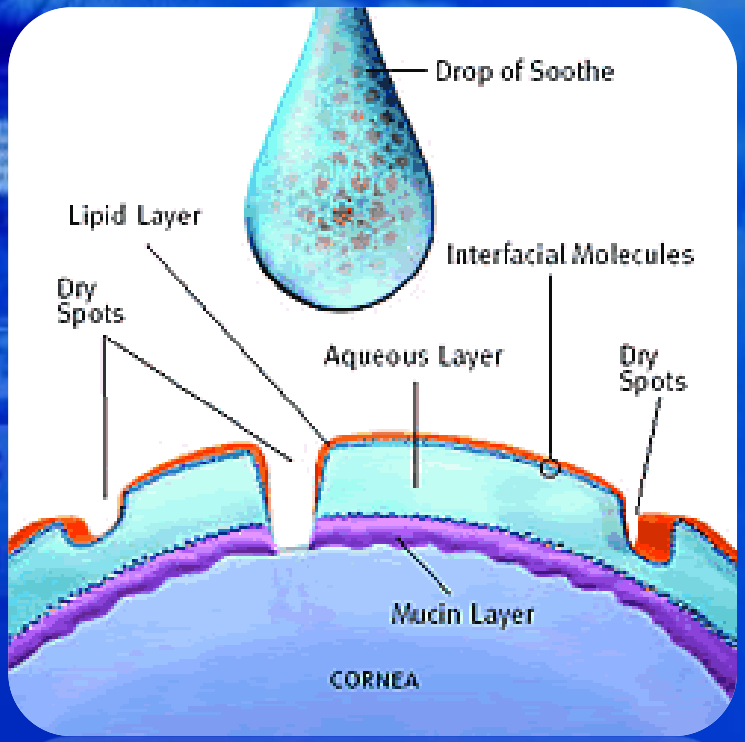
Local Anesthetics

- Orbital infiltration
  - peribulbar or retrobulbar
  - cause anesthesia and akinesia for intraocular surgery
  - e.g. lidocaine, bupivacaine



Other Ocular Preparations

- Lubricants
  - drops or ointments
  - Polyvinyl alcohol, methylcellulose or hyaluronic acid
  - Preserved or preservative free



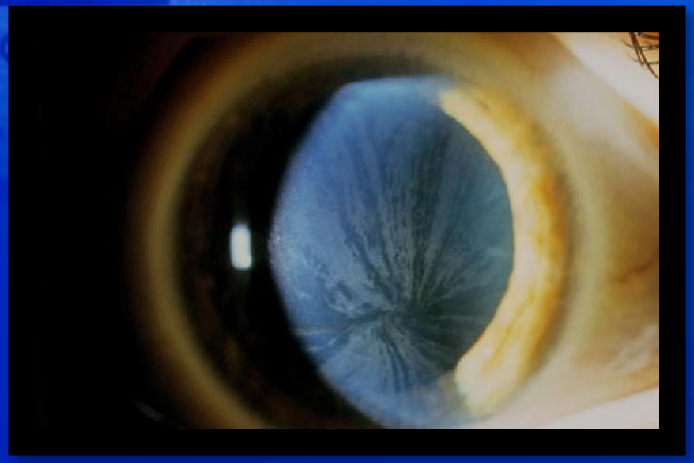
Ocular Toxicology

Complications of Topical Administration

- Mechanical injury from the bottle e.g. corneal abrasion
- Pigmentation: epinephrine-adrenochrome
- Ocular damage: e.g. topical anesthetics, benzalkonium preservative
- 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

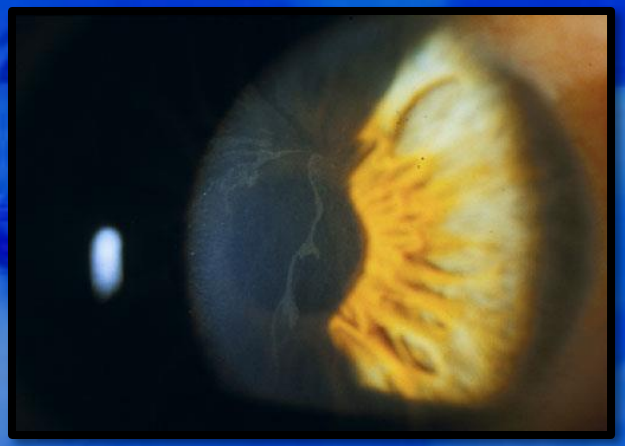
- A cardiac failure drug
- Causes chromatopsia (objects appear yellow) with overdose

French market scene viewed with no color deficiency

French market scene viewed with xanthopsia

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)



Chlorpromazine

- A psychiatric drug
- Causes corneal punctate epithelial opacities, lens surface opacities. Reversible with drug discontinuation
- Pigmentary retinopathy in high doses

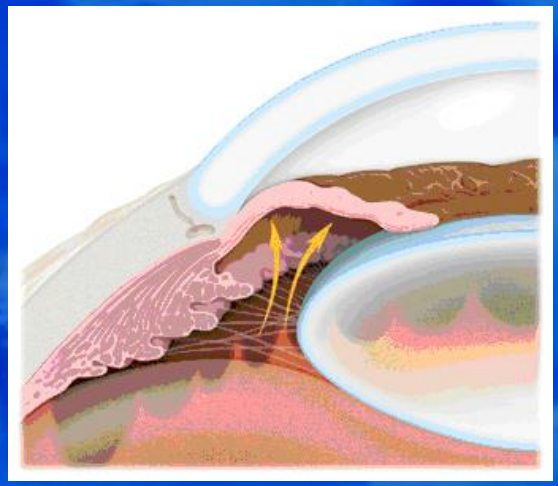
Thioridazine

- A psychiatric drug
- Causes a pigmentary retinopathy after high dosage

Phenytoin

- An epilepsy drug
- Causes dosage-related cerebellar-vestibular effects:
  - Horizontal nystagmus in lateral gaze
  - Diplopia, ophthalmoplegia
  - Vertigo, ataxia
- Reversible with the discontinuation of the drug

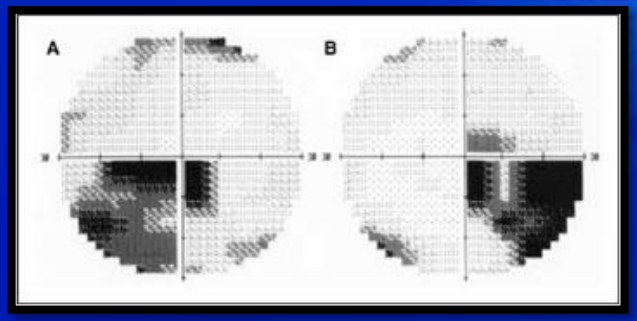
Topiramate

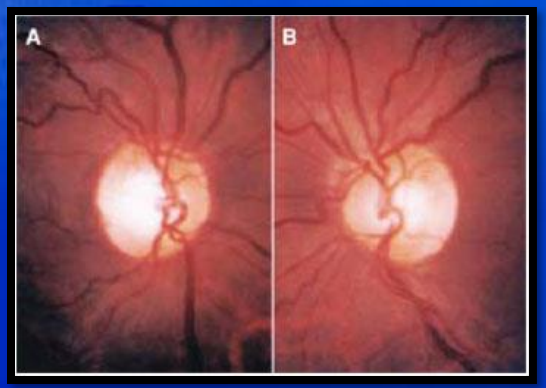


- A drug for epilepsy
- Causes acute angle-closure glaucoma (acute eye pain, redness, blurred vision, haloes).
- Treatment of this type of acute angle-closure glaucoma is by cycloplegia and topical steroids (rather than iridectomy) with the discontinuation of the drug

Ethambutol

- An anti-TB drug
- Causes a dose-related optic neuropathy
- Usually reversible but occasionally permanent visual damage might occur





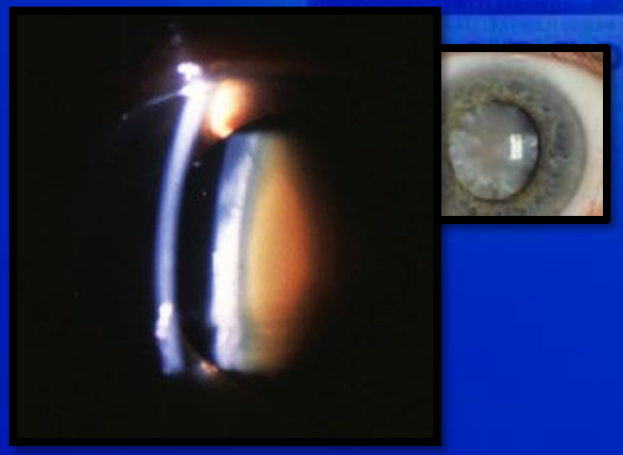
Agents That Can Cause Toxic Optic Neuropathy

- Methanol
- Ethylene glycol (antifreeze)
- Chloramphenicol
- Isoniazid
- Ethambutol
- Digitalis
- Chloroquine
- Streptomycin
- Amiodarone
- Quinine
- Vincristine and methotrexate (chemotherapy medicines)

- 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
- 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)
- Hypervitaminosis A – yellow skin and conjunctiva, pseudotumor cerebri (papilledema), retinal hemorrhage.
- Hypovitaminosis A – night blindness (nyctalopia), keratomalacia.

Thank you