

Ocular pharmacology and toxicology



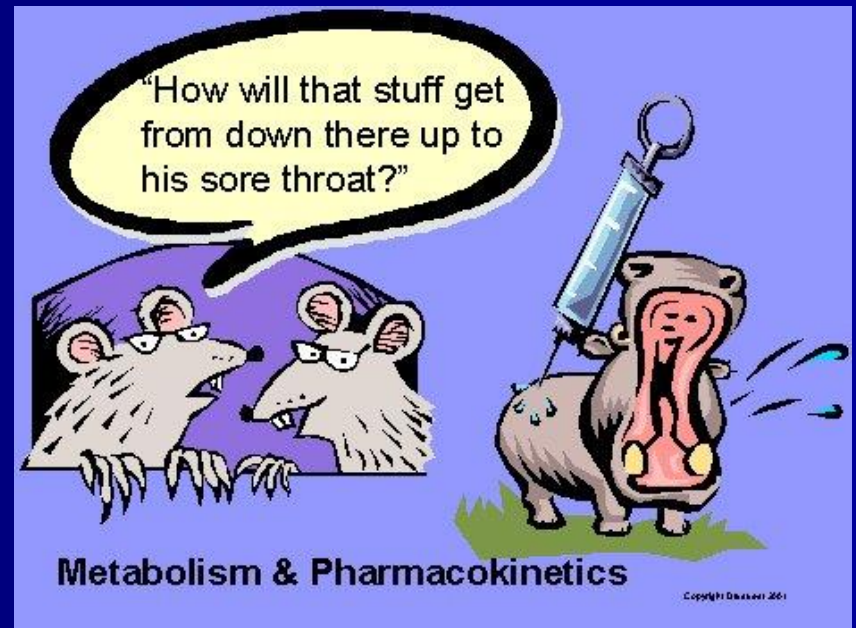
General pharmacological principles

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

- It is the absorption, distribution, metabolism, and excretion of the drug
- 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
- **Drug tonicity:** when an alkaloid drug is put in relatively alkaloid medium, the proportion of the uncharged form will increase, thus more penetration

Eye drops



- Eye drops- **most common**
- one drop = 50 μ l
- volume of conjunctival cul-de-sac 7-10 μ l
- 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

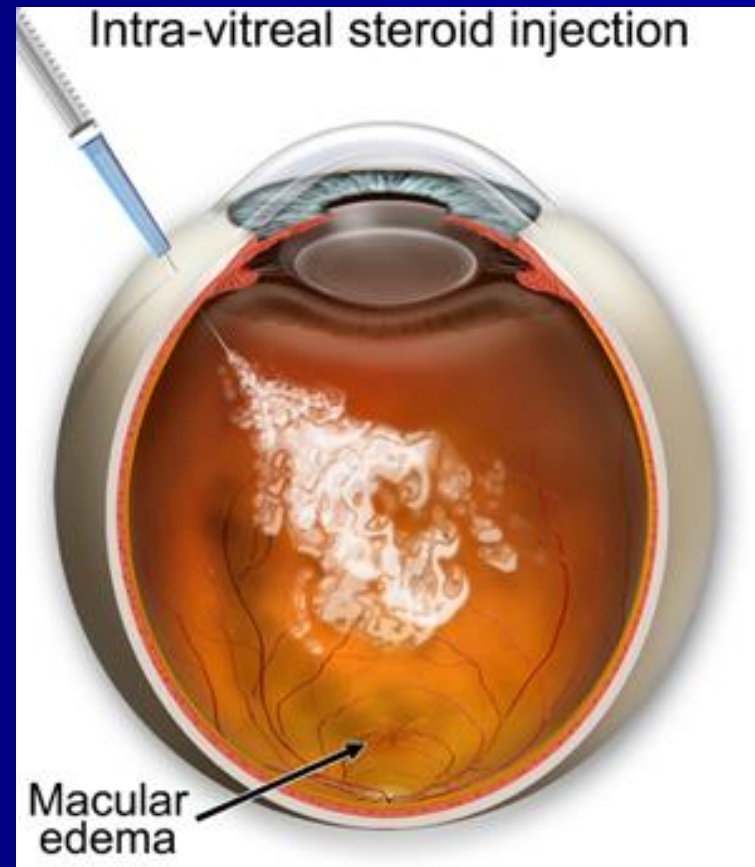
Peri-ocular injections

- 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. penicillins)
- Also steroid and local anesthetics can be applied this way



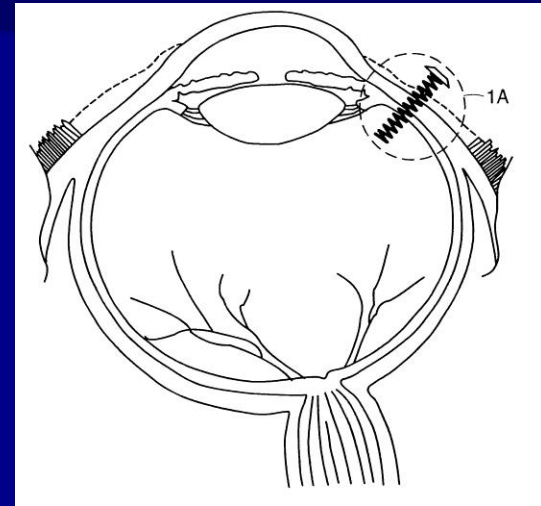
Intraocular injections

- Intracameral or intravitreal
- E.g.
 - Intracameral acetylcholine (miochol) during cataract surgery
 - Intravitreal antibiotics in cases of endophthalmitis
 - Intravitreal steroid 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.
 - Ocusert delivering pilocarpine
 - 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 pharmacotherapeutics

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

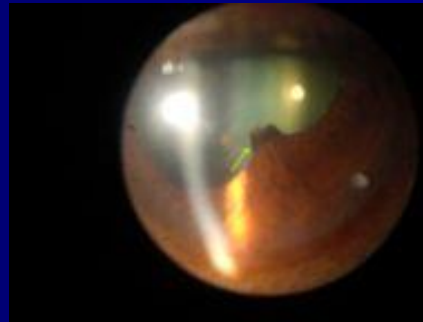
Cholinergic agonists

- 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:** funduscopy, 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 delirium
 - 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 adrenochochrome**, cystoid macular edema in aphakic eyes
 - C/I in closed angle glaucoma



Adrenergic agonists

- Alpha-1 agonists
- E.g. phenylephrine
- **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

Alpha adrenergic antagonists

- E.g. thymoxamine, dapiprazole
- **Uses:** to reverse pupil dilation produced by phenylephrine
- Not widely used

Beta-adrenergic blockers

- E.g.
 - non-selective: timolol, levobunolol, metipranolol, carteolol
 - 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, dichlorphenamide, dorzolamide, brinzolamide.
- **Uses:** glaucoma, cystoid macular edema, pseudotumour 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, unoprostone
- **Uses:** glaucoma
- **Mechanism:** increase uveoscleral aqueous outflow
- **Side effects:** darkening of the iris (heterochromia iridis), lengthening and thickening of eyelashes, intraocular inflammation, macular edema



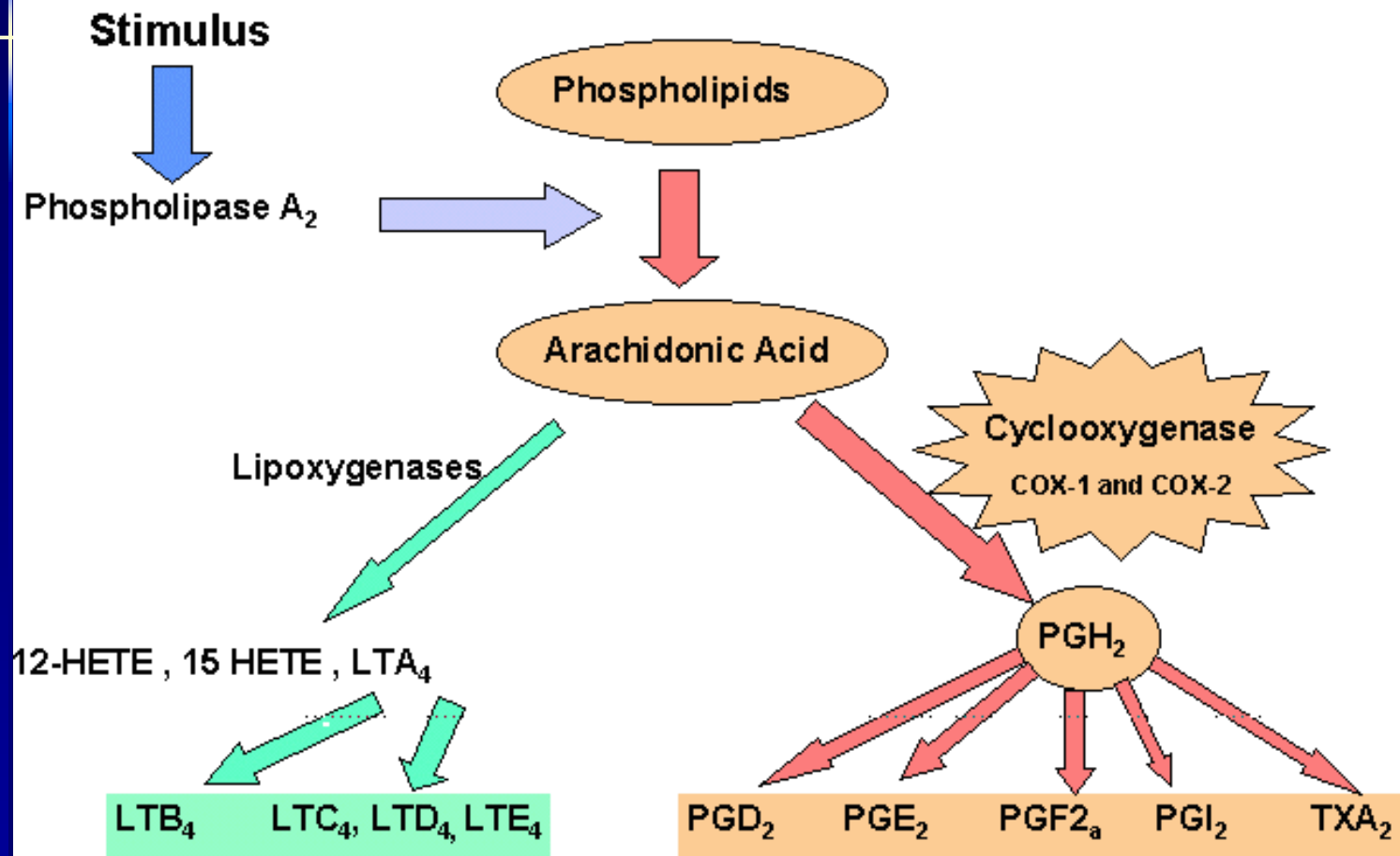
Anti-inflammatory

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graph TD; A[Anti-inflammatory] --> B[corticosteroid]; A --> C[NSAID]
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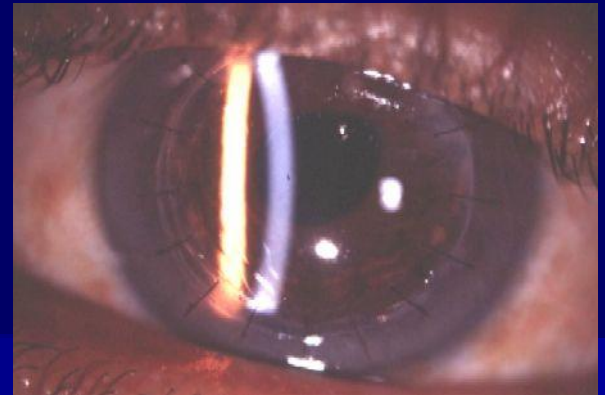
corticosteroid

NSAID

Figure 2 : Biosynthesis of eicosanoids



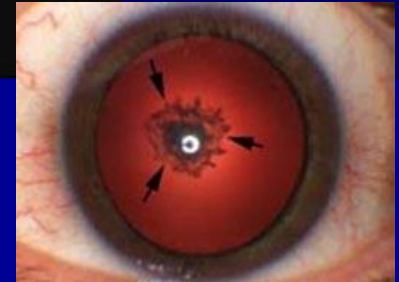
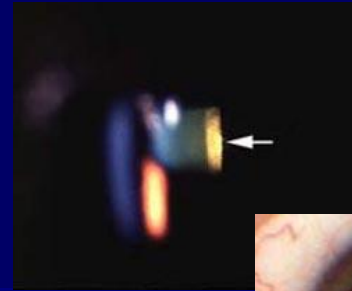
Corticosteroids



■ Topical

- E.g. fluorometholone, remixelone, 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, ptosis, mydriasis, scleral melting, skin atrophy

Corticosteroids



■ Systemic:

- E.g. prednisolone, cortisone
- **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

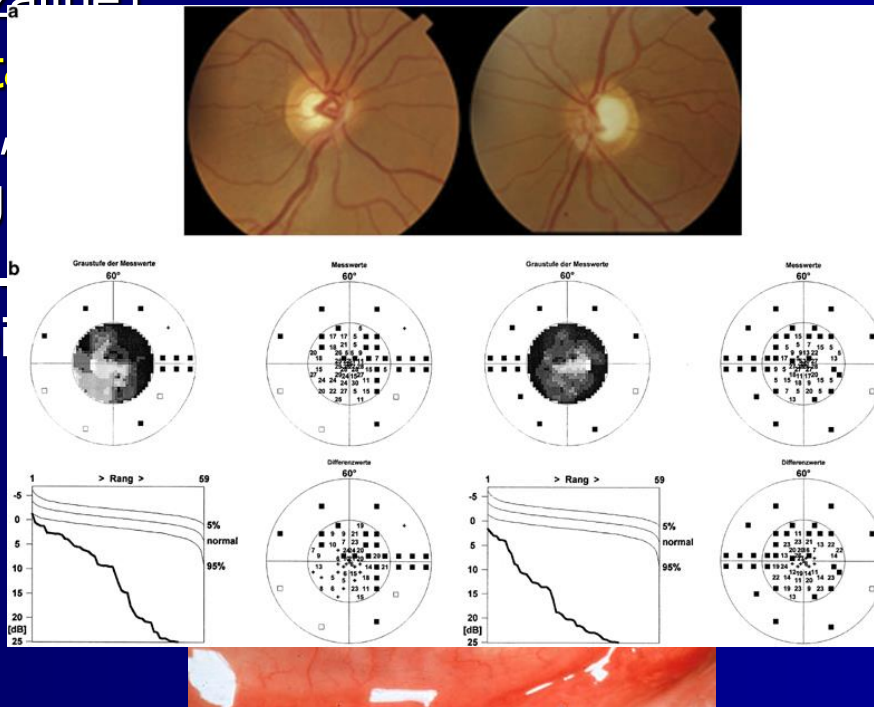
NSAID



- E.g. ketorolac, diclofenac, flurbiprofen
- **Mechanism:** inactivation of cyclo-oxygenase
- **Uses:** postoperatively, mild allergic conjunctivitis, episcleritis, mild uveitis, cystoid macular edema, preoperatively to prevent miosis during surgery
- **Side effects:** stinging

Anti-allergics

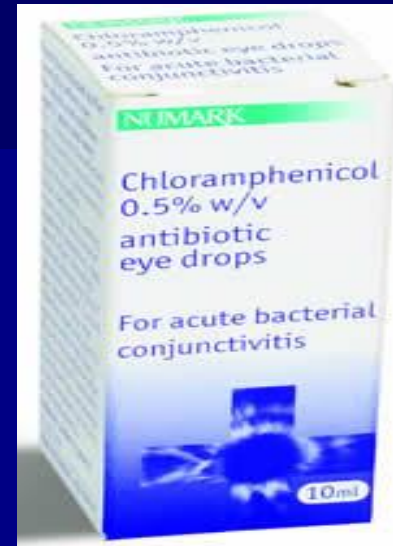
- Avoidance of allergens, cold compress, lubrications
- **Antihistamines** (e.g. pheniramine, levocabastine)
- **Decongestants** (e.g. naphazoline, phenylephrine, tetrahydrozoline)
- **Mast cell stabilizers** (e.g. nedocromil, cromoglycate)
- **NSAID** (e.g. ibuprofen)
- **Steroids** (e.g. beclomethasone, fluticasone, mometasone, budesonide, flunisolide)
- Drug combinations



epimirolast,
nisolone)

Antibiotics

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



Antibiotics

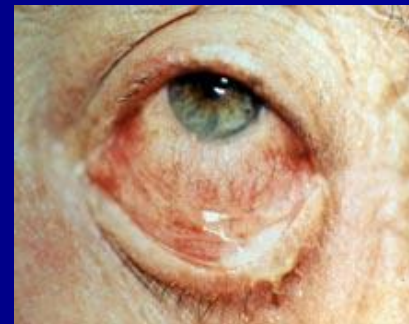
- Used **topically** in prophylaxis (pre and postoperatively) and treatment of ocular bacterial infections.
- Used **orally** for the treatment of preseptal cellulitis e.g. amoxicillin with clavulonate, cefaclor
- Used **intravenously** for the treatment of orbital cellulitis e.g. gentamicin, cephalosporin,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



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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

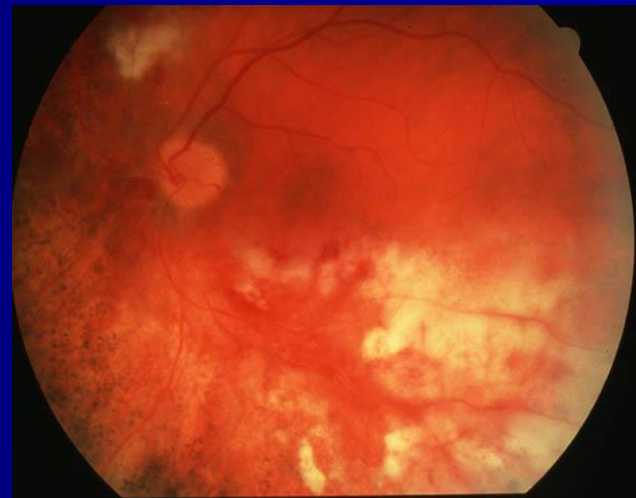
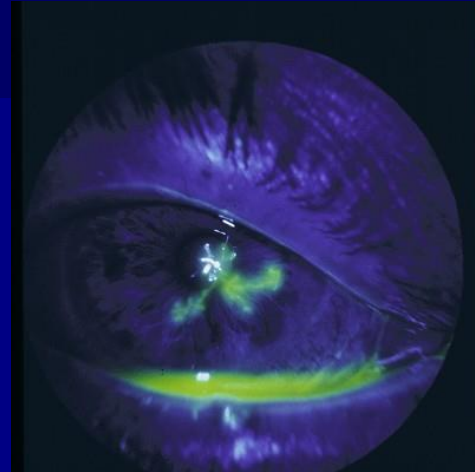


Antifungals

- **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

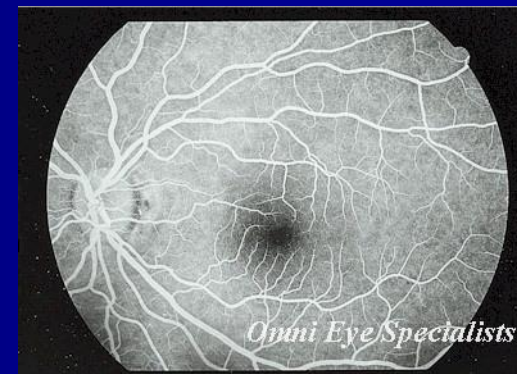
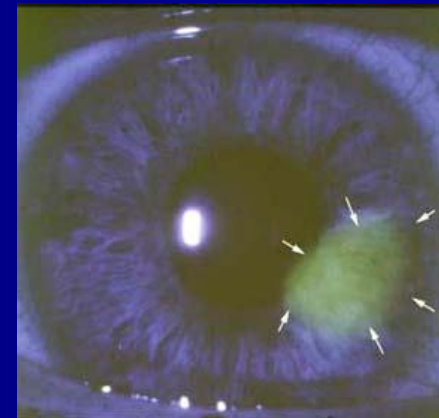
Antivirals

- **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



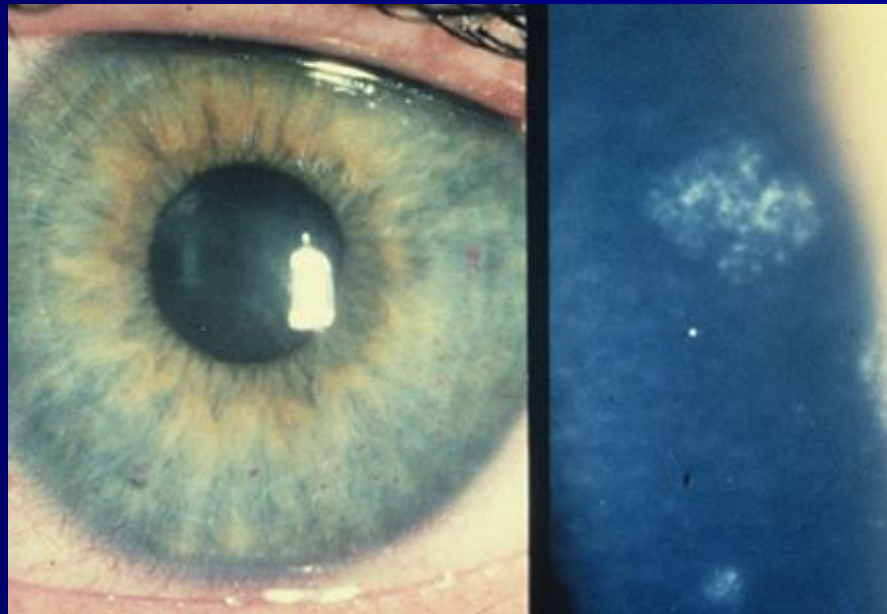
Ocular diagnostic drugs

- 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, gonioscopy, 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

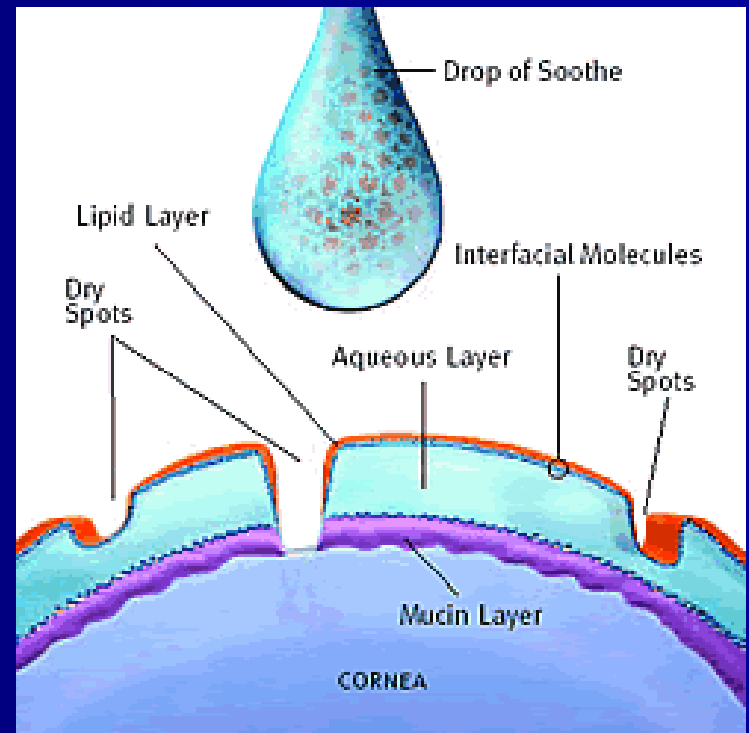
- Orbital infiltration
 - peribulbar or retrobulbar
 - cause **anesthesia** and **akinesia** for intraocular surgery
 - e.g. lidocaine, bupivacaine



Other ocular preparations

■ Lubricants

- drops or ointments
- Polyvinyl alcohol, cellulose, methylcellulose
- Preserved or preservative free



Intraviteal injection

- Anti-VEGF
(vascular endothelial growth factor)
 - Bevacizumab (Avastin),
Ranibizumab (Lucentis),
Aflibercept (Eylea)

- Uses:
 - PDR, DME
 - CRVO, BRVO
 - Wet AMD (age-related macular degeneration)

Ocular toxicology

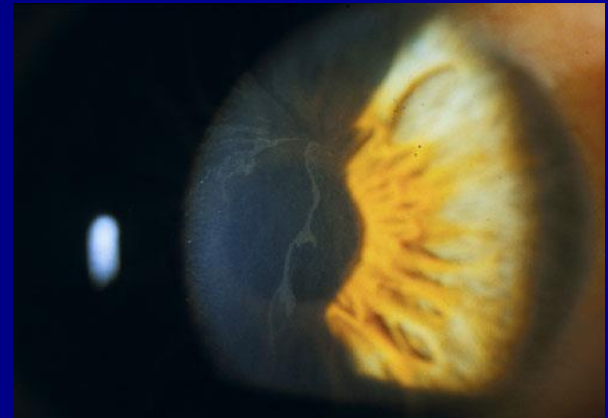
Complications of topical administration

- **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



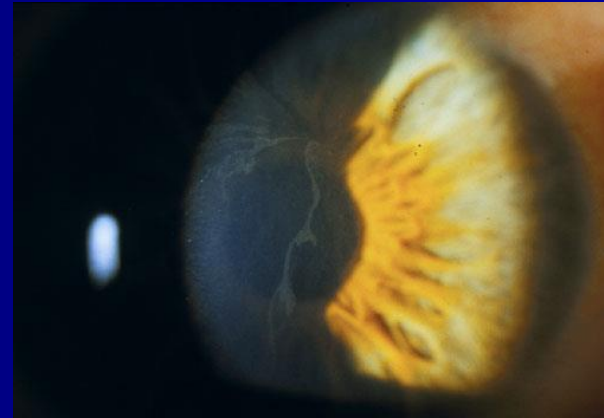
French market scene viewed with no color deficiency



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)

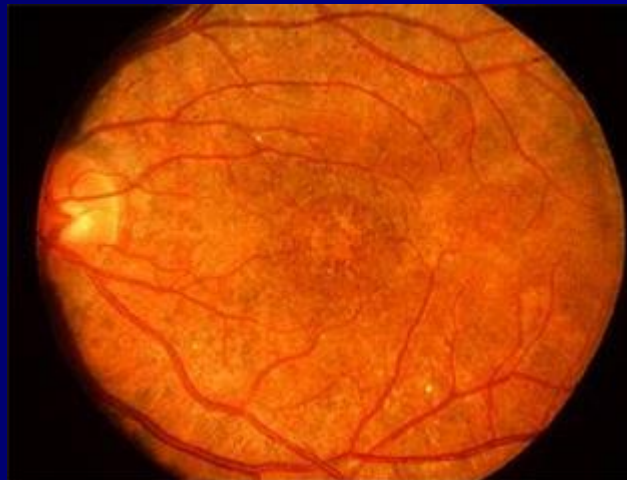


Chorpromazine

- A psychiatric drug
- Causes **corneal punctate epithelial opacities, lens surface opacities**
- Rarely symptomatic
- Reversible with drug discontinuation

Thioridazine

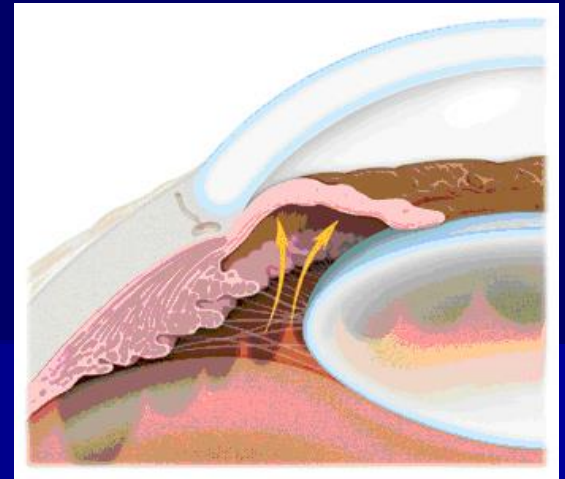
- A psychiatric drug
- Causes a **pigmentary retinopathy** after high dosage



Diphenylhydantoin

- 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

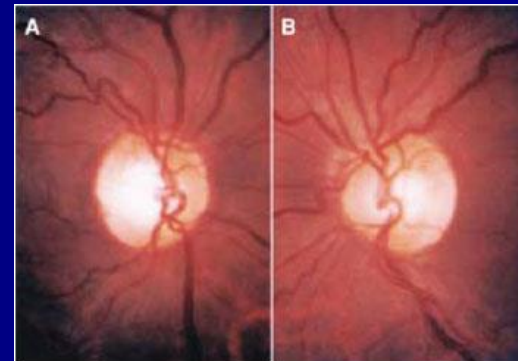
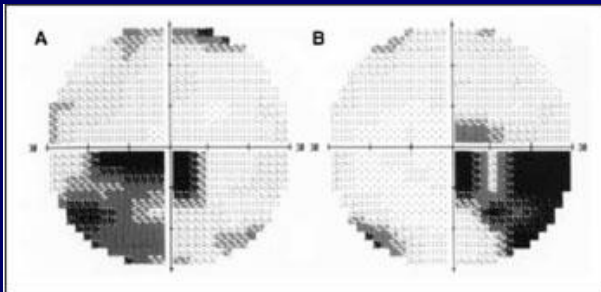
Topiramate



- 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

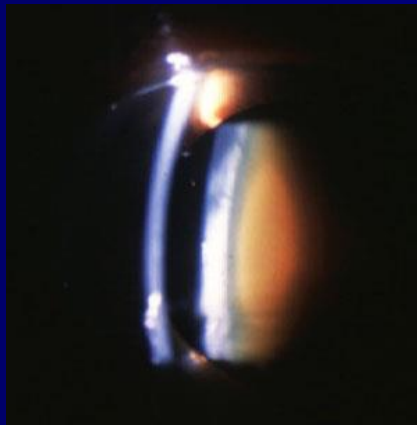


Agents that Can Cause Toxic Optic Neuropathy

- Methanol
- Ethylene glycol (antifreeze)
- Chloramphenicol
- Isoniazid
- Ethambutol
- Digitalis
- Chloroquine
- Streptomycin
- Amiodarone
- Quinine
- Vincristine and methotrexate (chemotherapy medicines)
- Sulfonamides
- Melatonin with Zoloft (sertraline, Pfizer) in a
- 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.

Thank you

A yellow speech bubble with a white outline and a tail pointing towards the bottom-left. It contains the text "Any question?".

Any question?