

430 Ophthalmology Team

1st lecture:

Ocular pharmacology and toxicology

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Note : b/c = because C/I contraindication BP= blood

General pharmacological principles

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 > activate the receptor or antagonist > opposite the action

■ 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 > around the globe

■ Intraocular injection > intra the globe

– 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% > 1% or 2% or and 3% is less effect than 4% same but 5% it will be less potent because of tearing reflex but limited by reflex tearing > more increase in the solution > more irritant to ocular tissue > at certain level there will be reflex tearing trying to wash out the concentrated medication .

■Viscosity: addition of methylcellulose and polyvinyl alcohol increases drug penetration by increasing the contact time with the cornea and altering corneal epithelium(normally there is a tight junction in the epithelium and by using viscosity material it will help loosing this tightness between tissue and have more effect) .
>Use the ointment .

■Lipid solubility: because of the lipid rich environment of the epithelial cell membranes, the higher lipid solubility the more the penetration and more effect .

Surfactants: the preservatives used in ocular preparations alter cell membrane in the cornea and increase drug permeability e.g. benzylkonium and thiomersal
Surfactants are materials that putting in the drug to keep it more staple .

■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 un charged (unionized) form will increase, thus more penetration

Eye drops

■Eye drops-most common > local drugs will be more effective and less side effects and its direct working in the target.

■one drop = 50 μ l

■volume of conjunctival cul-de-sac 7-10 μ l

■measures to increase drop absorption:

- if the pt use more than one drug > wait 5-10 minutes between drops
-compress lacrimal sac > b/c normally after tear secreted and cover the ocular surface it will be drain to naso-lacrimal duct so compression will prevent this mechanism .

-keep lids closed for 5 minutes after instillation > b/c plinking act as a pump mechanism for tearing that will go to nasal cavity .



Ointments

- Increase the contact time of ocular medication to ocular surface thus better effect
- It has the disadvantage of vision blurring > to avoid this advise pt to use it at night while sleeping
- 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 > used for more posterior targets
- E.g. subconjunctival, subtenon (tenon is fibrous sheath covering the sclera), peribulbar (bulbar mean globe so peri mean around), or retrobulbar (behind the globe)
- 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 > this is used in ER

Intraocular injections



■ **Intracameral** > injection in to anterior chamber or intravitreal > in to vitreous cavity.

Notes :

*Anterior chamber between the cornea and iris

*Posterior chamber between the iris and lens

■ E.g.

– Intracameral acetylcholine (miochol) during cataract surgery

– Intravitreal antibiotics in cases of endophthalmitis > it's infection of the vitreous cavity, its ER case , and need to manage quickly .it's a poor prognosis

– Intravitreal steroid in macular edema > its edema of the macula which is a center of vision could happen in many diseases like: diabetic retinopathy

– Intravitreal Anti-VEGF =(vascular endothelium growth factor) for DR=(diabetic retinopathy), other method is using intravitreal steroid

Sustained-release devices

■ These are devices that deliver an adequate supply of medication at a steady-state level (used for decrease the compliance e.g. instead of 4 times daily will be 2 times)

■ E.g.

– Ocusert delivering pilocarpine > used for glaucoma

– Timoptic XE delivering timolol > glaucoma

– Ganciclovir sustained-release intraocular device > anti viral ,it's a mechanical device ?

– Collagen shields > it's a contact lens that be absorbed by 24 h.

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

Because there is a blood ocular barrier that will be degraded when eye is inflamed, so more drug will be delivered to ocular tissue for that decrease the dose of the drug.

Ocular pharmacotherapeutics

Cholinergic agonists



<miosis

■ Directly acting agonists:

–E.g. pilocarpine, acetylcholine (miochol), carbachol (miostat)

–Uses: miosis > constriction of pupil uses in : glaucoma

–Mechanisms:

■ Miosis by contraction of the iris sphincter muscle

■ increases aqueous outflow through the trabecular meshwork > (it's a structure in the angle, it's responsible for drainage) by longitudinal ciliary muscle contraction that will pull the angle lead to increase the space more fluid will go out.

■ Accommodation by circular ciliary muscle contraction > change in the RE of the lens in order to see near objects

–Side effects:

■ Local: diminished vision (myopia), headache > b/c of ciliary muscle contraction that maintain for long time and cause pre-ocular pain, cataract, miotic cysts, and rarely retinal detachment

■systemic side effects: lacrimation, salivation, perspiration, bronchial spasm, urinary urgency, nausea, vomiting, and diarrhea

Cholinergic agonists : reversible and irreversible .

■Indirectly acting (anti-cholinesterases):

–More potent with longer duration of action

–Reversible inhibitors

■e.g. physostigmine

■used in glaucoma and lice infestation of lashes

Also used for masthina gravies .

■can cause CNS side effects for that not commonly used.

Indirectly acting (anticholinesterases):

–Irreversible:

■e.g. phospholine iodide

■Uses: in accommodative esotropia (inward deviation eye)

■side effects: iris cyst and anterior subcapsular cataract

■Contraindication: angle closure glaucoma, asthma, Parkinsonism

■causes apnea if used with succinylcholine or procaine.

* MCQ for that use non-depolarized muscle relaxant in general anesthesia



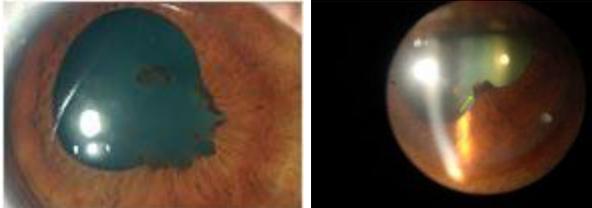
Cholinergic antagonists

Its orderd depend on the duration of actions:

■E.g. tropicamide (short duration 5-6h), cyclopentolate, homatropine, scopolamine, atropine (longest duration for 2 wk)

■Cause mydriasis (by paralyzing the sphincter muscle) with cycloplegia (by paralyzing the ciliary muscle will lead to inability for near vision and inability to read so you should aware the patient about it.

■ Uses: funduscopy > to examine the retina, cycloplegic refraction > to prevent the accommodation process to measure the refraction error correctly, anterior uveitis (its inflammation of the uvea which is 3 structures iris, ciliary body and choroid, in iritis, some inflammatory cells will enter the anterior chamber and cause adhesion btw the lens and iris and this is called posterior synechiae and for the anterior synechiae its between the iris and cornea).



pictures shows posterior synechiae

■ Side effects:

–local: allergic reaction, blurred vision because of the dilation.

–Systemic (cholinergic antagonist effects):nausea, vomiting, pallor, vasomotor collapse, constipation, urinary retention, and confusion

–specially in children they might cause flushing, fever, tachycardia, or delirium .

–Treatment by(DC= discontinue) or use of anti-dose physostigmine



* Usually anticholinergic drugs are with Red top bottle.



Adrenergic agonists

■ Non-selective agonists (α_1 , α_2 , β_1 , β_2)

–E.g. epinephrine, depevefrin > (pro-drug of epinephrine, its converting to epi by estraine enzyme in the epithelium of the cornea, its 17 more potent than epi)

–Uses: glaucoma

–Side effects: headache, arrhythmia, increased blood pressure, conjunctival adrenochrome ?, cystoid macular edema in aphakic eyes > (eye without lens)
*Pseudo-aphakic eye : pt with artificial lens after cataract surgery .

–C/I in closed angle glaucoma

Alpha-1 agonists

■E.g. phenylephrine

■Uses: mydriasis (without cycloplegia) > no ciliary paralysis so pt can read MCQ, decongestant > if pt have red eye

■Adverse effect:

–Can cause significant increase in blood pressure specially in infant and susceptible adults > MCQ

How ? naso-lacrimal duct to nasomucosa and absorbed there, or conjunctival vessels to circulation or by nasolacrimal to oropharynx

So this drug not giving to pt with HTN.

–Rebound congestion

–precipitation of acute angle-closure glaucoma in patients with narrow angles > not used in pt with narrow angle because it make the angle narrower >> more drainage impaired > increase in IOP.

Alpha-2 agonists

–E.g. brimonidine, apraclonidine

–Uses: glaucoma treatment, prophylaxis against IOP spiking after glaucoma laser procedures eg : peripheral iridotomy

–Mechanism: decrease aqueous production, and increase uveoscleral outflow > 10-20 % of drainage is happen by absorption of the fluid through uvea and sclera.

–Side effects:

■local: allergic reaction, mydriasis, lid retraction > molar muscle is supply by sympathetic so will be over activate MCQ, conjunctival blanching

■systemic: oral dryness, headache, fatigue, drowsiness, orthostatic hypotension, vasovagal attacks

–Contraindications: infants, MAO inhibitors users

*(MAO =Monoamine oxidate), why C/I ? Cause it may aggravate the BP.

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 > act on B1 and B2: timolol, levobunolol, metipranolol, carteolol

–selective: betaxolol (beta 1 “cardioselective”)

■Uses:glaucoma

■Mechanism: reduce the formation of aqueous humor by the ciliary body > Note : to decrease the IOP is either by increase the drainage or decrease the formation .

■Side effects: bronchospasm (less with betaxolol > selective) > C/I with asthmatic and COPD pt, cardiac impairment

Carbonic anhydrase inhibitors

■E.g. acetazolamide, methazolamide, dichlorphenamide, dorzolamide, brinzolamide.

■Uses: glaucoma > it suppress the aqueous , cystoid macular edema, pseudotumour cerebri> it’s increase in the CSF pressure without any tumor and it affect the eye and cause bilateral optic disc swelling.

■Mechanism: aqueous suppression

■Side effects: myopia, parasthesia (numbness), anorexia, GI upset, headache, altered taste and smell, Na and K depletion, metabolic acidosis, renal stone, bone marrow suppression “aplastic anemia”

■Contraindication: sulpha allergy >so not used in pt known to have sulfa allergy , digitalis users > b/c of risk of hypokalemia , pregnancy

Osmotic agents

Used to have sudden drop in IOP < immediate effect

■Dehydrate vitreous body

how it's work?

By this drug we are loading circulation by high amount of fluid ,so the fluid will escape from low concentration (vitreous) to high concentration (circulation) which reduce IOP significantly

■E.G. Oral

–glycerol 50% syrup (cause nausea, hyperglycemia) > and hyperosmolarity or keto-acidosis , don't forget to check the pt blood sugar before giving this drug .

–Mannitol 20% IV (cause fluid overload and not used in heart failure) > because the fluid will move from intra cellular to extra cellular compartment .Don't forget to assess the heart before giving this drug

Prostaglandin analogues

■E.g. latanoprost, bimatoprost, travoprost, unoprostone

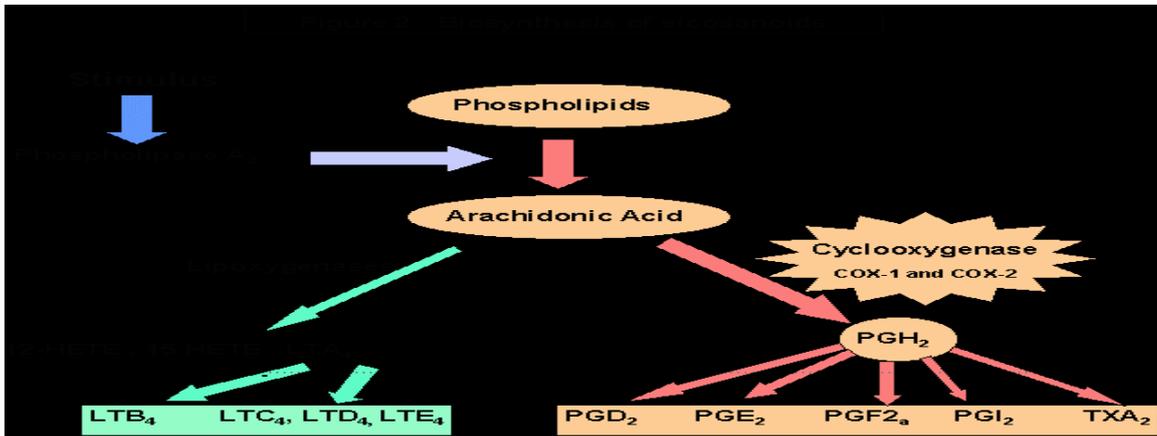
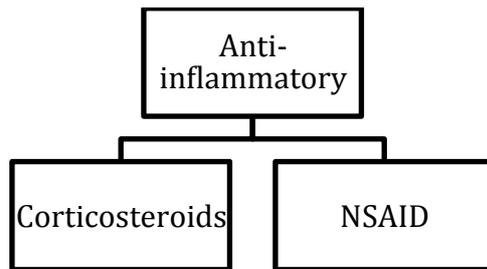
■Uses:glaucoma

■Mechanism:increase uveoscleral aqueous outflow

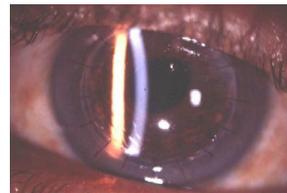
■Side effects:darkening of the iris (heterochromia iridis), lengthening and thickening of eyelashes, intraocular inflammation, macular edema



This picture show heterochromia iridis



Corticosteroids



This picture show keratoplasty

■ Topical

–E.g. fluorometholone, rimexolone, prednisolone, dexamethasone, hydrocortisone

–Mechanism: inhibition of arachidonic acid release from phospholipids by inhibiting phospholipase A₂

–Uses: postoperatively, anterior uveitis, **only severe allergic** conjunctivitis, vernal keratoconjunctivitis, prevention and suppression of corneal graft rejection, episcleritis (inflammation of the tissue surrounding the sclera), scleritis (inflammation of the sclera)

–Side effects: susceptibility to infections < **b/c of decrease the immunity**, glaucoma > **its serious b/c the IOP will increase gradually and pt will not know so you should follow up the pt and check IOP**, cataract, ptosis, mydriasis, scleral melting, skin atrophy

Systemic:

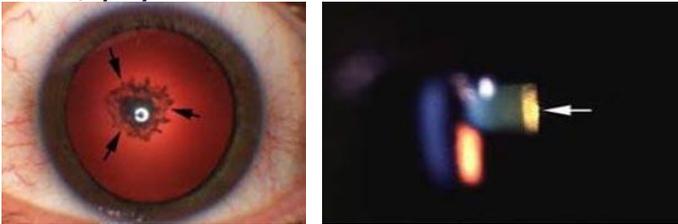
–E.g. prednisolone, cortisone

–Uses:posterior uveitis, optic neuritis> pt with MS, temporal arthritis with anterior ischemic optic neuropathy

–Side effects:

■Local: posterior subcapsular cataract < its more with systemic corticosteroid , glaucoma < its more with local corticosteroid, central serous retinopathy

■Systemic: suppression of pituitary-adrenal axis> for that stop the drug gradually to allow the body to produce his own steroid, 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>very common حرقان

Anti-allergics

■Avoidance of allergens< 1st line treatment, cold compress, lubrications

■Antihistamines(e.g.pheniramine, levocabastine)

■Decongestants(e.g. naphazoline, phenylephrine, tetrahydrozaline)

■Mast cell stabilizers(e.g. cromolyn, lodoxamide, pemirolast, nedocromil, olopatadine)

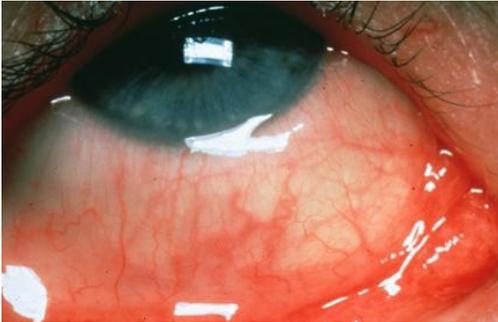
*Usually use a combination of antihistamine and mast cell stabilizers

■ NSAID(e.g. ketorolac)

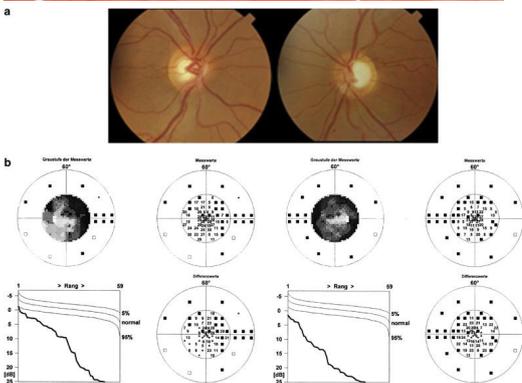
■ Steroids(e.g. fluorometholone, rimexolone, prednisolone)

Use in severe cases but because of side effect not giving to all pt.

■ Drug combinations



< picture show chemosis



< picture show cupping field defect

Antibiotics

■ Penicillins

■ Cephalosporins

■ Sulfonamides

■ Tetracyclines

■ Chloramphenicol

■ Aminoglycosides

■ Fluoroquinolones

■ Vancomycin

■ macrolides

■ 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 > more ER case because the infection could cause encephalitis, meningitis

e.g. gentamicin, cephalosporin, vancomycin, flagyl

■ Can be injected intravitally for the treatment of endophthalmitis

In this picture :

pt have a cataract surgery, severe pain and redness and puss is in the ant. chamber (hypopyon).



Andrew Doan, MD, PhD
U of Iowa 2004

It's Endophthalmitis < ER case the puss goes to vitreous cavity

Treated by : IV antibiotic that will cover g - and + directly to the vitreous cavity.

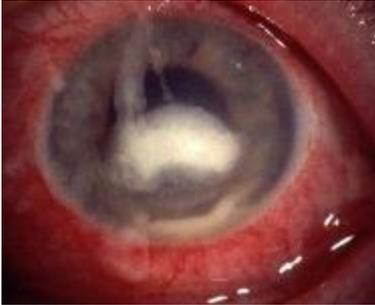
_Trachoma > its infection by *Chlamydia trachomatis*, can be treated by topical and systemic tetracycline or erythromycin, or systemic azithromycin.

■ Bacterial keratitis (bacterial corneal ulcers) > caused by trauma, contact lens infection may cause permanent scar can be treated by topical concentrated antibiotic frequently fortified penicillins, cephalosporins, aminoglycosides, vancomycin, or fluoroquinolones.

■ Bacterial conjunctivitis usually self limited but topical erythromycin, aminoglycosides, fluoroquinolones, or chloramphenicol can be used



This picture show Muco-purulent discharge with redness in the conjunctivae(bacterial conjunctivitis)



This picture show hypopyon (corneal ulcer)

Antifungals

■Uses: fungal keratitis, fungal endophthalmitis

■Polyenes

–damage cell membrane of susceptible fungi

–e.g. amphotericin B, natamycin

–side effect: nephro-toxicity > check the renal function before and after giving the drug.

■Imidazoles

–increase fungal cell membrane permeability

–e.g. miconazole, ketoconazole

■Flucytocine

–act by inhibiting DNA synthesis

Acyclovir

interact with viral thymidine kinase (selective)

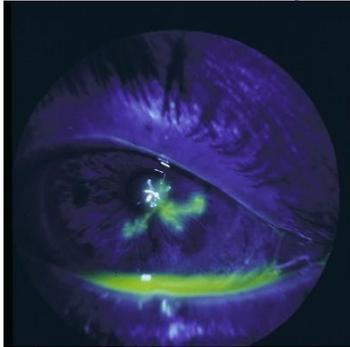
used in herpetic keratitis (inflammation of the cornea by herpes virus)

■ Trifluridine

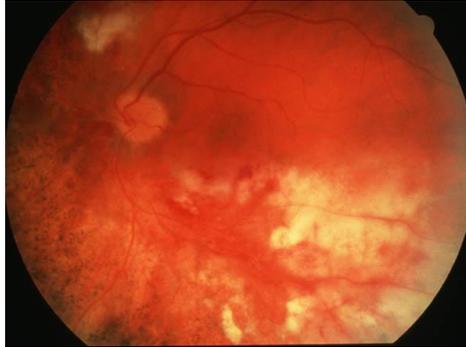
more corneal penetration
can treat herpetic iritis

■ Ganciclovir

used intravenously for CMV retinitis

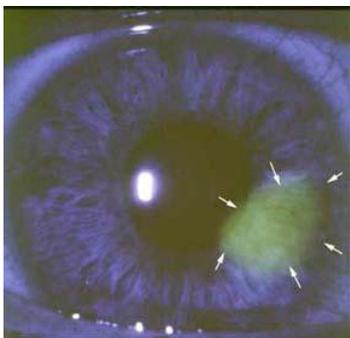


<Herpes

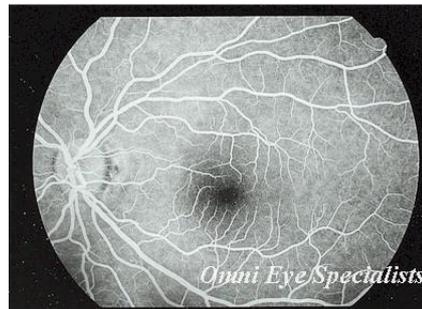


<CMV

Ocular diagnostic drugs



<abrasion stain



Fluorescein dye

–Available as drops or strips

–Uses: stain corneal abrasions, applanation tonometry, detecting wound leak, NLD
(naso-lacrimal duct) obstruction > the effected eye will take more time to drainage
, fluorescein angiography

–Caution:

■ stains soft contact lens > remove the contact lens

■Fluorescein drops can be contaminated by Pseudomonas sp > not common these days because now we use single one for each pt.



Rose bengal stain

–Stains devitalized epithelium

–Uses: severe dry eye, herpetic keratitis in early stage.

Local anesthetics

■topical> drop

–E.g. propacaine, tetracaine

–Uses:applanation tonometry > to avoid the corneal reflex , 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

Orbital infiltration

–peribulbar or retrobulbar

–cause anesthesia and akinesia for intraocular surgery

–e.g. lidocaine> short acting, bupivacaine > longer acting

Other ocular preparations

■Lubricants

–drops or ointments

–Polyvinyl alcohol, cellulose, methylcellulose

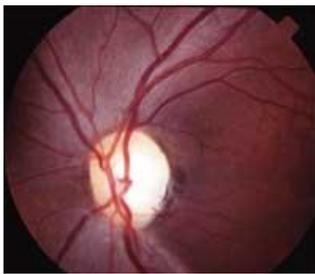
–Preserved or preservative free

Ocular toxicology

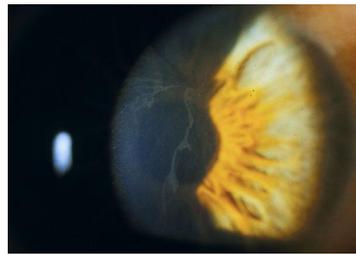
Complications of topical administration

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

Amiodarone



< optic neuropathy



< corneal verticillata

■ 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



French market scene viewed with no color deficiency



French market scene viewed with xanthopsia

■ A cardiac failure drug

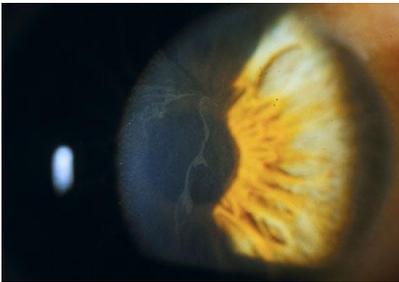
■ Causes chromatopsia (objects appear yellow) with overdose

*Chromatopsia is reversible .

Chloroquines



< bull's eye maculopathy



< corneal verticillata

■ 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) >

Pt should be follow up to check the retina , any abnormality seen then stop the drug and change it

Chorpromazine

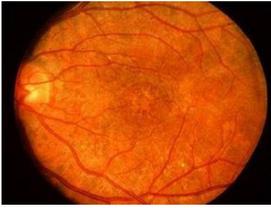
■ A psychiatric drug

■ Causes corneal punctate epithelial opacities, lens surface opacities

■ Rarely symptomatic

■ Reversible with drug discontinuation

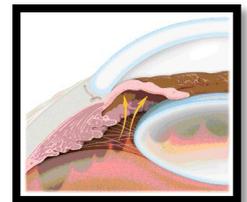
Thioridazine



- A psychiatric drug
- Causes a pigmentary retinopathy (salt and pepper) after high dosage

Diphenylhydantoin

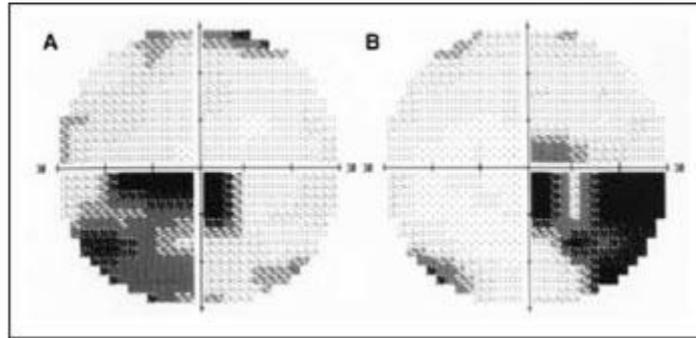
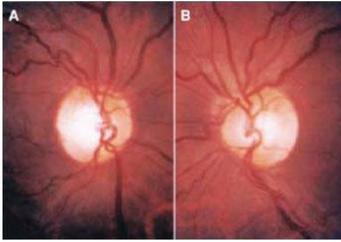
- An epilepsy drug
- Causes dosage-related cerebellar-vestibular effects:
 - Horizontal nystagmus in lateral gaze
 - Diplopia, ophthalmoplegia
 - Vertigo, ataxia
- Reversible with the discontinuation of the drug



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

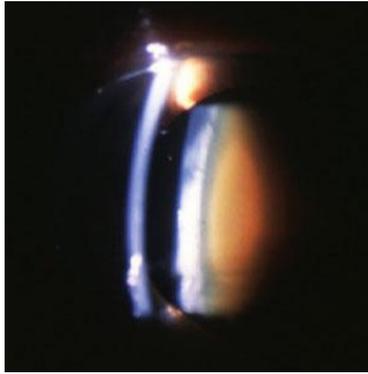


- An anti-TB drug
- Causes a dose-related optic neuropathy > follow up the pt monthly .
- Usually reversible but occasionally permanent visual damage might occur

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).

reductase inhibitors (statins)



< both pictures show cataract .

■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.