Ocular Pharmacology & Toxicology

Objectives:

- Not Given

[Color index : Important | Notes | Extra]

Resources: Slides + 433 team + Notes
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General pharmacological principles

Pharmacodynamics:

- **Mechanism of action:** it's the biological and therapeutic effect of the drug.
- Most drugs act by binding to regulatory macromolecule, usually neurotransmitters or enzymes or hormone receptors.
- 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 : how the drug reach particular area and how it will be execrated.
- **A drug can be delivered to ocular tissue as:**

<table>
<tr>
<td rowspan="2">Locally</td>
<td>Eye Drops

We prefer local on systemic b/c of more effect on target tissue and less side effects
 
</td>
<td>

Most commonly used , best way ,can use it during day time.

one drop = 50 µl , more than third of the drug will wash out so one drop is more than enough.
volume of conjunctival cul-de-sac (is the fornix of conjunctiva that act as reservoir of drug) 7-10 µl

Measures to increase drop absorption , so increase effect :

Wait 5-10 minutes between drops , it will decrease diluted effect.
Compress lacrimal sac, that will decrease systemic effect.
Keep lids closed (blinking sucks the fluid from the ocular surface and drain it to the nasal cavity that's why we till the patient to close his eyes) for 5 minutes after instillation , increase local effect and decrease systemic effect

doesn't reach in high concentrate behind the lense
once you the bottle , if it preserved like in fridge you can use it till expiry date , it it outside the fridge then you can use for 1 month only

</td>
</tr>
<tr>
<td>Ointments

  </td>
<td>

Increase the contact time of ocular medication to ocular surface thus better effect. More viscous = stays for longer time
It has the disadvantage of <u>vision blurring</u> (advise pt to put it before going to sleep)
The drug has to be high lipid soluble with some water solubility to have the maximum effect as ointment.
it cover the eye at the bed time.

Note: eye drops and ointments likely to affect anterior segment of the eye (cornea , conjunctiva , anterior chamber , the iris , lens and posterior chamber but not any further so we need to use injection around the eye or directly to the eye.
</td>
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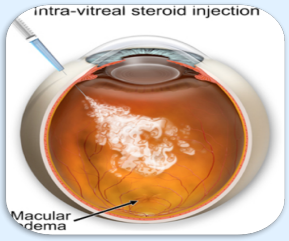
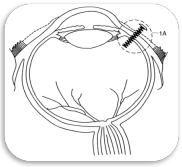
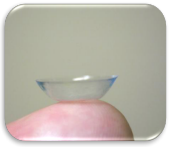
</table>

	Peri-ocular injections 	• Reach behind iris-lens diaphragm better than topical application. e.g. subconjunctival, subtenon (capsule surround the sclera and behind conjunctiva), peribulbar (around the globe), or retrobulbar (behind the globe) • This route bypass the conjunctival and corneal epithelium : good for drugs with low lipid solubility (e.g. penicillins) • Also steroid (reduce inflammation) and local anesthetics can be applied this way • Use it when higher concentration , longer duration wanted in the anterior chamber so inject behind the eye , and use it in critical condition like Endophthalmitis which is (inflammation inside the eye) and give antibiotic • Use short needle or you will puncture the glop.
	Intraocular injections 	• Intracameral (anterior chamber) or intravitreal, e.g: delivers the medication directly into the eye ○ Intracameral acetylcholine (miochol) during cataract surgery During cataract surgery, we put a lens inside the eye. How can we access the area behind the iris? We dilate the pupil > access the lens > aspirate it > put a lens. In order to secure the lens in position, we inject acetylcholine into the eye (parasympathomimetics) > constricts the pupil and luck the lens. ○ Intravitreal antibiotics in cases of endophthalmitis a true ocular emergency that happens when an organism reaches the vitreous cavity and releases endotoxins that destroy the ocular tissue. Giving an antibiotic ASAP is essential. ○ Intravitreal steroid in macular edema (diabetic patients) ○ Intravitreal anti-VEGF (vascular endothelial growth factor) for DR. the most recent method of treating diabetic retinopathy.
	Sustained- release devices	• These are devices that deliver an adequate supply of the medication at a steady-state level ,e.g.: These devices increase patients compliance by decreasing the frequency of administration 1. Ocusert delivering pilocarpine. 2. Timoptic XE delivering timolol. 3. Ganciclovir sustained-release intraocular device. Antiviral (CMV retinitis in cases of immunocompromised patients). We implant it surgically. 4. Collagen shields. Dissolve in 2-3 hrs while the contact lens will not dissolve. 5. Liposomes.  
Systemic	• Oral or IV. • Factor influencing systemic drug penetration into ocular tissue: 1. **Lipid solubility of the drug:** more penetration with high lipid solubility , Major factor : more lipid binding less effect. Lipid solubility is favorable in case of systemic medications 2. **Protein binding:** more effect with low protein binding. More protein binding = will not go to ocular tissue 3. **Eye inflammation:** more penetration with ocular inflammation. If the eyes are inflamed, there will be degradation of blood ocular barrier which prevents the systemic medication from going to the eye Which means more systemic medication goes to ocular tissue. so , when the eye is inflamed, we decrease the dose.	

Factors influencing local drug penetration into ocular tissue:

Drug concentration:	The higher the concentration the better the penetration e.g. pilocarpine 1-4%. If you increase the concentration of a solution > more strong & more irritant to the ocular tissue > release of tears. So they are testing different amounts of concentrations and they reach certain concentration beyond which the irritation will be less.
Viscosity:	Higher viscosity increases drug penetration by: ● Increasing the contact time with the cornea. ● Altering corneal epithelium. More penetration to the ocular tissue.
Lipid solubility:	The higher lipid solubility the more the penetration (lipid rich environment of the epithelial cell membranes). (more lipophilic = more diffusion to the ocular tissue = more effect of the medication).
Surfactants	The preservatives used in ocular preparations alter cell membrane in the cornea and increase drug permeability e.g. benzalkonium and thimerosal. Simply, surfactants are preservatives > preservative is a compound added to medications to make these medications stable for certain period of time. There are some medications with or without preservatives. Preservatives alter (loosen) the junction between the cell membranes, so there will be more diffusion of the medication to the ocular tissue.
pH:	the normal tear pH is 7.4 and if the drug pH is much different, this will cause **reflex tearing**. Both acidic or alkaline are not desirable because both will be identified by the eye as irritants.
Drug tonicity	When an alkaloid drug is put in relatively alkaloid medium, the proportion of the uncharged form will increase, thus more penetration. The non-ionized form of the medication is the active form. So if you want a non-ionized drug, you should make it more ALKALINE (~7.5, not so far from 7.4)

Ocular pharmacotherapeutics:

Cholinergic agents (agonists)

Directly acting agonists: [e.g. pilocarpine, acetylcholine]

Indirectly acting (anticholinesterases) : More potent with longer duration of action (act by binding to cholinesterase, the inhibition of this enzyme could be reversible or irreversible)

Uses: To Induce miosis, for glaucoma.

Mechanisms:

- Miosis by contraction of the iris sphincter muscle. (constriction of the pupil). It causes miosis by direct contraction of iris sphincter muscle which is supplied by parasympathetic NS.
- Accommodation by circular ciliary muscle contraction. A change in lens refractive power in order to see the nearer objects.
- Increases aqueous outflow (inside eye to outside) through the trabecular meshwork by longitudinal ciliary muscle contraction. Contraction of the longitudinal ciliary muscle > the spaces in trabecular meshwork will open > more fluid will go to the circulation

Side effects:

- Local: diminished vision (**myopia** with long use), headache (continuous contraction of the ciliary muscle), cataract, miotic cysts, and rarely retinal detachment.
- **Systemic side effects:** diarrhea, lacrimation, salivation, perspiration, bronchospasm, nausea, vomiting and urinary urgency.

Reversible inhibitors [e.g. Physostigmine used in Myasthenia Gravis]. Less potent, not commonly used.

- Used in glaucoma and lice infestation of lashes.

We use it to treat glaucoma as it increase the aqueous outflow (drainage to the circulation = less fluid in the eye = less pressure).

- Side effect: CNS side effects.

Irreversible inhibitors [e.g.phospholine iodide].

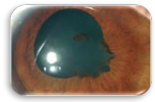
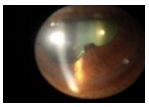
- Used in **accommodative esotropia**.

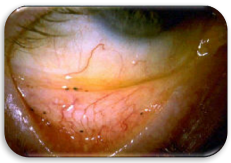
- Esotropia = Eyes in
- Exotropia = Eyes out
- These children are usually hypermetropic which means that the image is formed behind the retina.
- Accommodation increases the refractive power of the eye and brings the image from behind the retina to the retina.
- When someone accommodates or changes his refractive power 2 things happen: 1) miosis 2) conversion. (eyes will go in). So, when these children try to accommodate, the 2 things (miosis&conversion) happen. This explains why they have esotropia.
- We use this medication to induce accomodation without actively having the child to accommodate himself.

(they have strabismus when focusing in typically farsightedness)

- Side effect: iris cyst and anterior subcapsular cataract.
- Contraindicated : in angle closure glaucoma, asthma, Parkinsonism -causes apnea if used with succinylcholine or procaine. Use atracurium as an alternative.

Contraindications: asthma, Parkinsonism

Cholinergic antagonists	
Examples	Tropicamide (6 hrs), cyclopentolate, homatropine, atropine (10-14 DAYS)
Cause	Mydriasis (by paralyzing the sphincter muscle) with cycloplegia (by paralyzing the ciliary muscle (so there will be loss of accommodation)
Uses	Fundoscopy, cycloplegic refraction (procedure to measure the refractive error by temporarily paralyzing the muscles that aid in the accommodation because if there is accomodation the result would be wrong glass prescription.Thus, measurement will be precise.), anterior uveitis.
Side effects	• local: allergic reaction, blurred vision especially in bright light • 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 as an antidote  

Adrenergic agonists: be careful for: cardiac disease, asthma and BP			
Types	**Non-selective agonists** (α_1, α_2, β_1, β_2) E.g. epinephrine, dipivefrin (prodrug of epinephrine)	**Alpha-1 agonists** (e.g. phenylephrine)	**Alpha-2 agonists** (e.g. brimonidine, apraclonidine)
Uses	Glaucoma	**Mydriasis (without cycloplegia)** for fundus evaluation, they do not have effect on the ciliary muscle, decongestant because it is a vasoconstrictor. ★ WHAT IS THE MEDICATION THAT CAUSES MYDRIASIS WITHOUT CYCLOPLEGIA?	glaucoma treatment [treatment of the open angel not the closure angle] and prophylaxis after glaucoma laser procedures We use it to decrease IOP by decreasing the aqueous production and increasing the outflow **Mechanism:** decrease aqueous production, and increase uveoscleral (drainage 90% by canal of schlemm, 10%outflow uveoscleral) most of the drainage happen through trabecular meshwork (conventional). This medication affects only the uveoscleral one.
Side effects	Headache, arrhythmia, increased blood pressure, conjunctival adrenochrome (pigments/black dots in conjunctival fornix in pt use adrenergic drugs chronic users of epinephrine)"pic", cystoid macular edema in aphakic (without lens) eyes. phakic=lens, pseudophakic= artificial lens  Pic : notice the small dots if present, you have to ask about these drug, the dots are dangerous because it is a pigmentation lesion.	• Can cause significant increase blood pressure especially in infant and susceptible adults • Rebound congestion • Induce acute angle-closure glaucoma in patients with narrow angles	• **Local**: allergic reaction, mydriasis, lid retraction (it activates sympathetic which innervates muller muscle). ★ In the exam: pic & asking which eye is using alpha 2 agonist? The more opened eye. • **Systemic**: oral dryness, headache, fatigue, drowsiness, orthostatic hypotension, vasovagal attacks
Contraindications	Contraindication :in closed angle glaucoma can cause crowdening of the angle , cardiac patient.	Cardiac patient	**Contraindications**: infants because of their CNS side effects, MAO inhibitors users tendency to increase BP

			MAO : monoamine oxidase inhibitors for depression

Adrenergic antagonists	
Alpha adrenergic antagonists	**Beta-adrenergic blockers**
E.g. thymoxamine, dapiprazole	**E.g.** • **Nonselective:** timolol, carteolol • **Selective:** betaxolol (beta 1 "cardioselective") (Good for asthmatic)
Uses: to reverse pupil dilation produced by phenylephrine (better not to be used because of the risk of retinal detachment) **Not widely used**	**Uses**: glaucoma (commonly used to treat glaucoma because of their action on reducing the formation of aqueous by ciliary body)
	Mechanism: reduce the formation of aqueous humor by the ciliary body.
	Side effects: bronchospasm (less with betaxolol) (non-selective:exacerbates bronchial asthma, COPD) , cardiac impairment

Carbonic anhydrase inhibitors	
Examples	• acetazolamide, dorzolamide
Mechanism	• **aqueous suppression (carbonic anhydrase have a role in producing aqueous humor)**
Uses	• glaucoma, cystoid macular edema, **pseudotumor cerebri** Increased ICP without the presence of a tumor, we use it to decrease production of CSF.
Side effects	• myopia, **paresthesia** circumoral numbness and peripheral numbness , GI upset, headache, altered taste and smell , Na and K depletion, metabolic acidosis normal anion gap, renal stone, bone marrow suppression "aplastic anemia".
Contraindications	• sulfa allergy it's sulfa derivative, digitalis user's lethal hypokalemia, pregnancy

Osmotic Agents
(Used to suppress IOP as fast as possible in Acute attacks): Dehydrate vitreous body which reduce IOP significantly loading the circulation with high concentration of fluid > less conc. In the vitreous > the water will go from lesser to higher concentration, we are basically dehydrating the vitreous. E.G. are:

1. Glycerol 50% syrup (cause nausea, hyperglycemia) oral, caution in uncontrolled DM
2. Mannitol 20% IV (cause fluid overload, avoid in heart failure) (evaluate CVS before use)

- Use in case of acute angle closure glaucoma to reduce IOP rapidly.

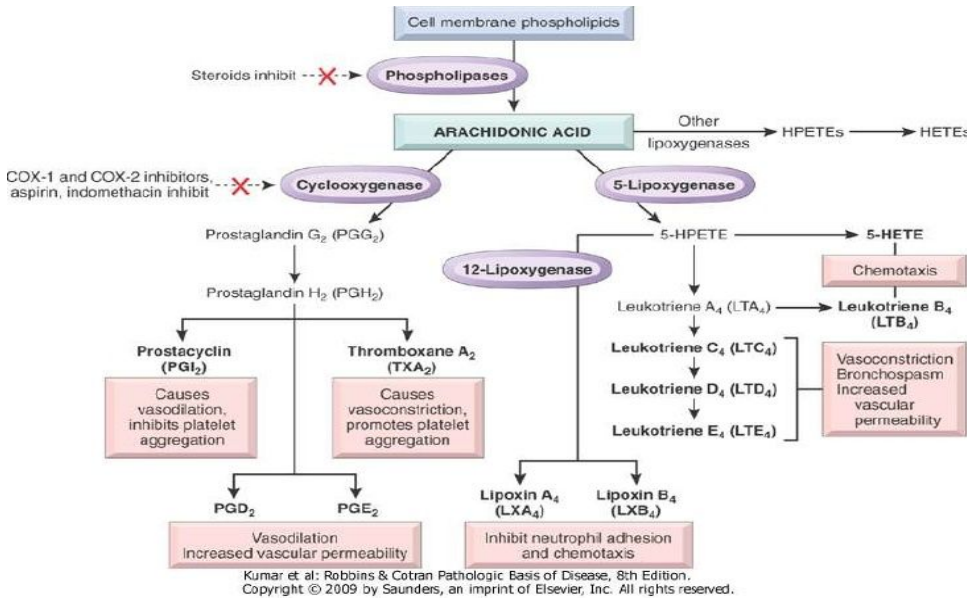
Prostaglandin analogues

- **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 because it's an inflammatory mediator, macular edema.

Anti-Inflammatory

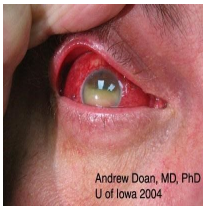
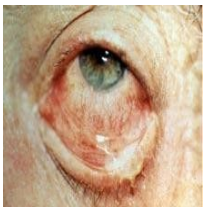
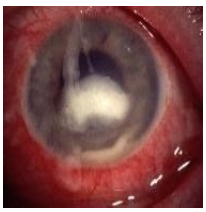
	Corticosteroids		NSAIDS
	Topical	**Systemic**	
Example	• Fluorometholone • remixolone • prednisolone • Dexamethasone • hydrocortisone	• Prednisolone • cortisone	• ketorolac, • Diclofenac • flurbiprofen
uses	• Postoperatively • Anterior uveitis • Severe allergic conjunctivitis we don't use it as 1st line, only if other medications failed. • Vernal keratoconjunctivitis • Prevention and suppression of corneal graft rejection • Episcleritis • Scleritis	• Posterior uveitis • Optic neuritis • Temporal arteritis with anterior ischemic optic neuropathy.	• Postoperatively • Mild allergic conjunctivitis • Episcleritis • Mild uveitis • Cystoid macular edema • Preoperatively to prevent miosis during surgery "to inhibit prostaglandin which is known to constrict the pupil"
Mechanism	• inhibition of arachidonic acid release from phospholipids by **inhibiting phospholipase A2** (very potent)		• **Inactivation of cyclooxygenase enzyme** (prevent formation of PG which causes miosis, so we use it in cataract surgery)
Side Effects	• Susceptibility to infections • **glaucoma** • **cataract** • Ptosis • Mydriasis • Scleral melting • Skin atrophy • **The most serious side effect of**	• Local: **posterior subcapsular cataract**, glaucoma, central serous retinopathy • Systemic: suppression of pituitary-adrenal axis, hyperglycemia, osteoporosis, peptic ulcer, psychosis	• Stinging.

	topical steroids is increased IOP (STEROID INDUCED GLAUCOMA) asymptomatic, permanent damage.		



Anti Allergics (Patient must present with itching; Avoid allergens, cold compress, lubrications)			
Type	**Example**	**Mechanism and Uses**	**Side Effect**
Antihistamines	• Pheniramine • levocabastine	Work by **blocking histamine** that is produced by the body in response to allergens or irritants	• Drowsiness. • bradycardia and overdose may lead to sleep disorders.
Decongestants	• naphazoline • phenylephrine • tetrahydrozoline	used to relieve redness, puffiness, and itchy/watering eyes due to colds, allergies, or eye irritations	• Stinging. • Redness. • widened pupils, or blurred vision.
Mast cell stabilizers	• cromolyn, • lodoxamide • pemirolast • nedocromil • olopatadine	They **block a calcium channel** essential for mast cell degranulation, stabilizing the cell and thereby **preventing the release of histamine** and related mediators.	
NSAID	• Ketorolac	-	• Stevens Johnson syndrome.
Corticosteroids	• Fluorometholone • remixolone • prednisolone	-	• Posterior subcapsular cataract. • Glaucoma. • Papilledema. • Predisposition to fungal

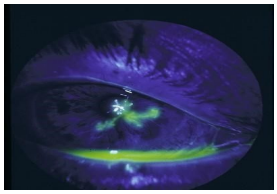
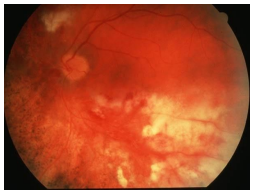
			infections.

Antibiotic	
Examples	Penicillins, Tetracyclines,Fluoroquinolones,Cephalosporins,Chloramphenicol,Vancomycin Sulfonamides,Aminoglycosides,Macrolides.
Uses	• 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 clavulanate, cefaclor. If there is an inflammation or infection in front of orbital septum > preseptal cellulitis > we use oral antibiotics. If the inflammation or infection is behind this septum > orbital cellulitis > a true ophthalmic emergency that can progress to meningitis or encephalitis or cavernous sinus thrombosis or periosteal abscess, that's why we treat it aggressively with **IV** antibiotics + admit the patient.  • Used **intravenously** for the treatment of orbital cellulitis e.g. gentamicin, cephalosporin, vancomycin, flagyl. • Can be injected **intravitreally** for the treatment of endophthalmitis.a true ophthalmic emergency that has to be treated by injecting the antibiotic directly to the eye, otherwise nothing can help! Hypopyon (collection of pus in the anterior chamber) is a sign of endophthalmitis.  • **Trachoma** can be treated by topical **and** systemic tetracycline or erythromycin, or systemic azithromycin. Caused by chlamydia trachomatis • **Bacterial keratitis** (bacterial corneal ulcers) can be treated by topical fortified penicillins, cephalosporins, aminoglycosides, vancomycin, or fluoroquinolones "hourly". Keratitis = cornea, there will be opacity. It can affect the vision permanently. Treat it with TOPICAL Abx EVERY HOUR even if the pt is sleeping.  • **Bacterial conjunctivitis** is usually self-limited but topical erythromycin, aminoglycosides, fluoroquinolones, or chloramphenicol can be used. Broad spectrum Abx

Anti-Fungal

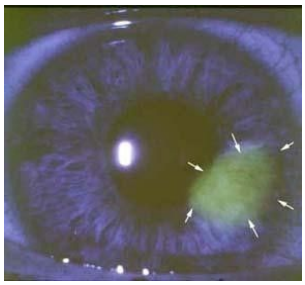
- **Uses:** fungal keratitis, fungal endophthalmitis.
- **Polyenes:**
  - Damage cell membrane of susceptible fungi.
  - E.g. amphotericin B, natamycin.
  - Side effect: nephrotoxicity.
- **Imidazoles:**
  - Increase fungal cell membrane permeability.

- E.g. miconazole, ketoconazole.
- **Flucytosine:**
  - Act by inhibiting DNA synthesis

Antiviral	
Acyclovir	■ interact with viral thymidine. ■ Kinase (selective). ■ Used in herpetic keratitis. **This picture could come in the exam > Stained eye showing dendritic shape ulcer > herpetic keratitis.** 
Trifluridine	■ **More** corneal penetration. ■ Can treat herpetic iritis.
Ganciclovir	Used intravenously for **CMV Retinitis.** Immunocompromised pts. 

Ocular diagnostic drugs:

1) **Fluorescein dye:** it goes to the area that doesn't have epithelium, so if the surface epithelium is deficient in some area,it will be stained by Fluorescein. Available as drops or strips
   - **Uses:** stain corneal abrasions, applanation tonometry to measure IOP, detecting wound leak, nasolacrimal duct obstruction If a patient came to you with tearing in the right eye, but the Fluorescein in the eye and check it after 5 minutes, after that, if you find more Fluorescein in the eye it means that the Fluorescein did not go to the nasal cavity means that there is some blockage in the nasolacrimal duct. That's how we diagnose NLD obstruction., fluorescein angiography I.V. > retinal circulation.



Caution!

o Stains soft contact lens. It will be stained permanently

o Fluorescein drops can be contaminated by Pseudomonas sp.

2) Rose Bengal Stain:

- Stains devitalized epithelium.
- Uses: severe dry eye, herpetic keratitis

Local anesthetics:

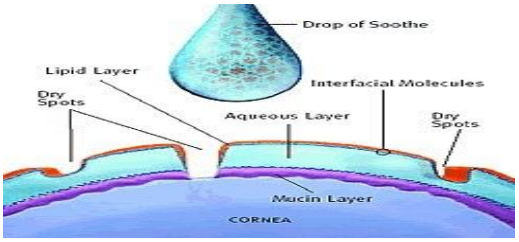
- **Topical:** E.g. proparacaine, tetracaine.
  - **Uses:** applanation tonometry, gonioscopy viewing the angle of the eye, removal of corneal foreign bodies, removal of sutures, examination of patients who cannot open eyes because of pain.
  - **Adverse effects:** toxic to corneal epithelium, allergic reaction rarely.

- **Orbital infiltration:** Peribulbar or retrobulbar.

  Cause anesthesia and akinesia for intraocular surgery. E.g. lidocaine, bupivacaine.

Lubricants:

- Drops or ointments.
- Polyvinyl alcohol, cellulose, methylcellulose.
- Preserved or preservative free. Less irritation

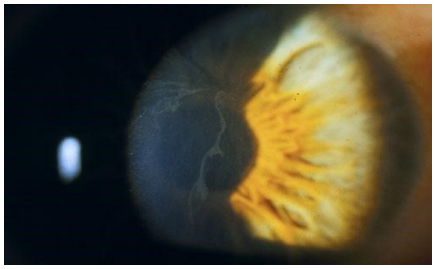
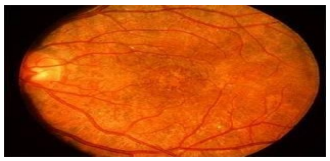


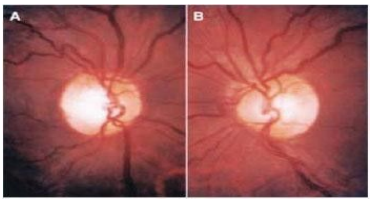
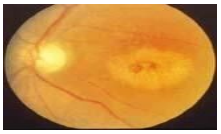
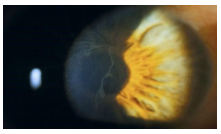
Ocular Toxicology:

❖ Complications of Topical Administration:

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

Drug	Effect

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.abnormal perception of color. If the object appears yellow > xanthopsia.  
Chlorpromazine	• 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 • **SALT AND PEPPER APPEARANCE** 
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, halos). • 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 
Chloroquine	• 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 & retinopathy **(bull's eye maculopathy)** • **vortex keratopathy could be caused by BOTH amiodarone and Chloroquine.**  

Agents that can cause Toxic Optic Neuropathy:

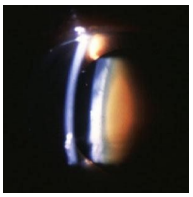
- **Methanol (IMP!!!)** Can cause bilateral blindness
- Ethylene glycol (antifreeze)
- Chloramphenicol
- Isoniazid
- high-protein diet
- Carbon monoxide
- Lead
- Mercury
- Ethambutol
- Digitalis
- Chloroquine
- Streptomycin
- Thallium (alopecia, skin rash,severe vision loss)
- Malnutrition with vitamin B-1 deficiency
- Amiodarone
- Quinine
- Methotrexate
- Pernicious anemia (vitamin B12 malabsorption phenomenon)
- Vincristine and methotrexate (chemotherapy medicines)
- Sulfonamides
- Melatonin with Zoloft (sertraline Pfizer)
- Radiation unshielded (exposure to >3,000 rads).

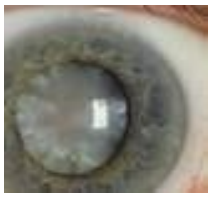
HMG-CoA REDUCTASE INHIBITORS (STATINS):

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 (Patient presents with history of alcohol drinking).
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.