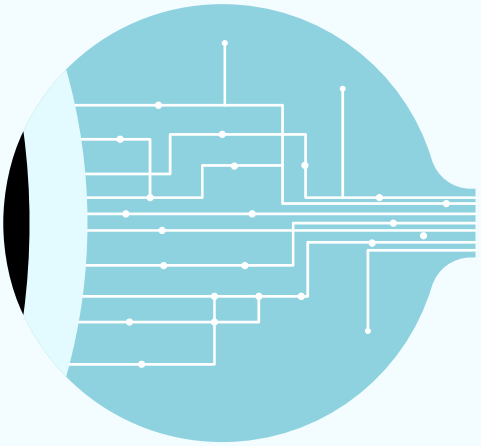
Lecture 11

v1.00



Ocular pharmacology and toxicology

Presented by: Dr. Abdullah Alkharashi

Objectives of the course:

- No objectives were found in the slides.
- This is the last ride :(

Color index:

Original content | Important | Golden Notes | Doctor's notes[439] | Doctor's notes[441] | Extra | Textbook

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 the eye.

Pharmacodynamics

- **Mechanism of action:** it is the biological and therapeutic effect of the drug.
- Most drugs act by binding to regulatory macromolecules, usually neurotransmitters, 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

- 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 the site of action is a function of the 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:

- Local:
  - Eye drops.(most common)
  - Ointment.
  - Peri-ocular injection.(peribulbar,subconjunctival)
  - Intraocular injection. (intravitreal,intracameral)
- 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%(why not 10%? The eye won't tolerate and will wash it out) but **limited** by reflex tearing. There is a limit after which the ocular surface will identify this solution as an irritant solution. So, If it is a concentrated solution, the eye try to have a defense mechanism (produce tearing in order to wash the concentrated solution) & thus will have less effect. you increase the concentration of a solution → more strong & more irritant to the ocular tissue → release of tears to wash this irritant material.
Viscosity	Addition of methylcellulose and polyvinyl alcohol increases drug penetration by **increasing the contact time** with the cornea and **altering corneal epithelium.** ➔ It loosens the tight junctions between the epithelium allowing the medication to penetrate more into the ocular tissue. ➔ Viscous material stays in the ocular tissue more than the solution. E.g. ointments
Lipid solubility	The higher the lipid solubility the more the penetration (because of the lipid rich environment of the epithelial cell membranes). The ocular surface is lipophilic and if the medication is lipophilic then there will be more penetration to the ocular tissue = more effect of the medication

General pharmacological principles

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. benzalkonium and thimerosal. Simply, surfactants are preservatives (compound added to medications to make these medications stable for certain period of time). Preservatives alter (loosen) the junction between the cell membranes, so there will be more diffusion and absorption 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 a relatively alkaloid medium, the proportion of the uncharged form will increase, thus more penetration. if you put a non-ionized medication into 7.4 and it is alkaloid (for example 7.8) then it will stay in a non-ionized form which is the active form of the medication, which will get absorbed and have the optimal effect. So if you want a non-ionized drug, you should make it more ALKALINE (~7.5, not so far from 7.4) . -if the drug is acidic → mostly ionized → most of it will be non-beneficial to the ocular surface.

Eye drops

- Most commonly used. (direct effect on target tissue and less systemic side effects)
  - One drop = 50 µl (micro is 10^{-6})(more than third of the drug will be washed out, so 1 drop is more than enough).
  - Volume of conjunctival cul-de-sac is 7-10 µl.
  - Only **20% of administered 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.

  - 3 Measures to increase drop absorption:
    - Wait 5-10 minutes between drops. (so one does not wash out the other)
    - Compress lacrimal sac (you prevent the drop from going into the nasal cavity so more will be retained in ocular tissue) that will decrease systemic effect.
    - Keep lids closed for 5 minutes after instillation (blinking works as a pump that sucks the tear from the ocular surface and drain it to the nasal cavity that's why we tell the patient to close his eyes).

General pharmacological principles

Ointments

- Increase the contact time of ocular medication to ocular surface thus better effect (more viscous = stays for longer time = more penetration).
- Preferred when the eye drops is difficult to apply e.g. kids
  - It has the disadvantage of **vision blurring** (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 an ointment.

Note: eye drops and ointments are more likely to affect anterior segment of the eye (cornea , conjunctiva, anterior chamber , the iris, lens and posterior chamber) but not any further, so if **posterior segment** of the eye is affected we need to use **injection around the eye** or **directly to the eye**.

Periocular injection

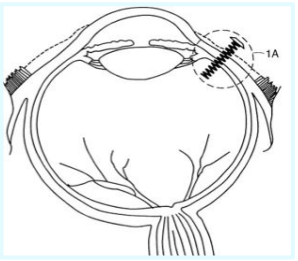
- We inject the medication around the globe into the orbital cavity
  - They reach behind iris-lens diaphragm (posterior uveitis) better than topical application e.g. subconjunctival, subtenon, peribulbar (around the globe → extraconal), or retrobulbar (behind the globe → intraconal).
  - This route bypass the conjunctival and corneal epithelium which is good for drugs with low lipid solubility (e.g. penicillins).
  - Also, steroid and **local anesthetics** (most common indication) can be applied this way. Xylocaine+ Marcaine combination.

Intraocular injections

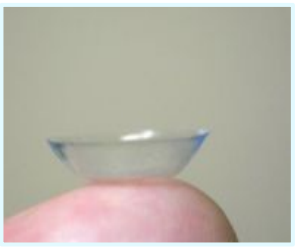
- Intracameral (into anterior chamber) or intravitreal (in the vitreous cavity) (it delivers the medication directly into the eye.)
- Examples:
  - Intracameral acetylcholine (miochol) during cataract surgery. (at the end of surgery)
    - In this surgery we aspirate the opacified lens & replace it with an artificial one; And in order to secure the lens in position, we inject acetylcholine into the eye, which is a cholinergic, to constrict the pupil (miosis).
  - Intravitreal antibiotics in cases of endophthalmitis a true ocular emergency that happens when an infection reaches the vitreous cavity. The organism multiplies and has toxins affecting the retina causing permanent damage. Eradicating the organism ASAP is essential.
    - Neither systemic administration nor topical administration reaches the vitreous cavity in a therapeutic concentration. So we inject it directly in the vitreous cavity to kill the organisms, endotoxins & limit the destruction of ocular tissue .
  - Intravitreal steroid in macular edema caused by diabetic retinopathy.
  - Intravitreal anti-VEGF (anti-vascular endothelial growth factor) for diabetic retinopathy (one of the recent treatment modalities for diabetic retinopathy). Or used for central vein occlusion and diabetic macular edema.

General pharmacological principles

Sustained-release device Skipped



- These are devices that deliver an adequate supply of a medication at a steady-state level.
  - Either pharmacological “drops” or mechanical devices used to increase patient’s compliance by decreasing the frequency of administration.
- Examples:
  - Ozerdex sustained release dexamethasone.
  - Ocusert delivering pilocarpine.
  - Timoptic-XE delivering timolol. in glaucoma.
  - Ganciclovir sustained-release intraocular device is a mechanical device that is implanted surgically for the treatment of CMV retinitis (antiviral).
  - Collagen shields are contact lenses that are soaked into the medication that we want to deliver to the ocular surface then worn. These collagen shields are absorbed within 12-24 hrs and the medication will be already delivered to ocular tissue.



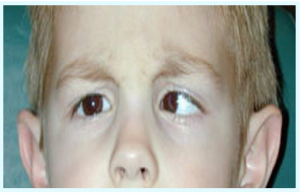
Systemic

- Oral or IV. (When do we use them? posterior segment or bilateral involvement of the eye / Autoimmune disease or TB Infection “the disease is outside the eye”/ or if there was a disease in the eye and I don’t want it to spread)
- Factors influencing systemic drug penetration into ocular tissue:
  - **Lipid solubility of the drug:** more penetration with high lipid solubility; Lipid solubility is favorable in case of systemic medications.
  - **Protein binding:** more effect with low protein binding.
  - **Eye inflammation:** more penetration with ocular inflammation. Because there will be degradation in eye blood ocular barrier so, when the eye is inflamed, we decrease the dose.

Ocular pharmacotherapeutics (Extra revision)

- Before starting you need to know the autonomic nervous system effect on the eye:
  - Sympathetic NS →
    - Pupil dilation “contraction of pupillary dilator or radial muscle”.
    - Decreases the production of aqueous humor.
    - Retraction of the eye “contraction of muller muscle”.
  - Parasympathetic NS →
    - Pupil constriction “contraction of pupillary constrictor or circular muscle”.
    - Increases the production of aqueous humor.
    - Accommodation: contraction of ciliary muscle → suspensory ligament will relax → the lens will be more curved → optical power of the lens will increase “this help in near object vision; it will bring the image on the retina”
- Accommodation is accompanied by 2 things: 1- convergence. 2- meiosis.
  - All of these bring the image on the retina.
  - As lens accommodation increases the refractive power, the convergence of the eyes will keep the image in the center of fovea.
  - Miosis increases the depth of focus of the eye by blocking the light scattered by the periphery of the cornea.
- **Note: Anti-glaucoma medication. Patient takes it for life**

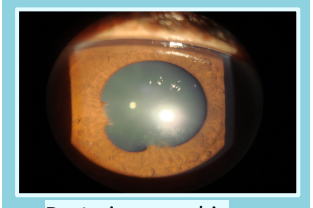
Cholinergic agonists

Cholinergic agonists	Directly acting agonists It binds to the receptor & is having same effect as the receptor.	Indirectly acting agonists " anti-cholinesterases " skipped They degrade cholinesterase enzyme which is available at the synaptic junction & is responsible for degradation of excess acetylcholine.Therefore, more acetylcholine will be available in the synaptic junction & thus more cholinergic effect.	
Examples:	• **Pilocarpine 1-4%** (can be used topically). Acetylcholine(miochol) (Intracameral) • Carbachol (miostat).	**Reversible inhibitors** **Physostigmine**. (also used for myasthenia gravis patients)	**Irreversible inhibitors** Phospholine iodide.
Uses:	▪ Miosis. ▪ Glaucoma. (Not anymore)	▪ previously used in Glaucoma ➔It increases the aqueous outflow (↑ drainage of the circulation = less fluid in the eye = ↓ pressure). ▪ Lashes of infestation lice. ➔It is not widely used because it has systemic side-effects - antidote for nerve gas	▪ Accommodative esotropia. - Rarely used 
Mechanisms of action:	▪ Miosis by contraction of the iris sphincter muscle (direct effect). ▪ Increases aqueous outflow (aqueous drainage) through the trabecular meshwork by longitudinal ciliary muscle contraction(↓IOP). ▪ Accommodation by circular ciliary muscle contraction.	▪ They are more potent with longer duration of action.	
Side-effects:	**Local:** ★ The 2 most common side effects of cholinergic agonists are **diminished vision** & **headache**. ★ **Diminished vision** because it induces **myopia**; the lens refractive power is increased & image will form in front of the retina.	▪ CNS side effects.	▪ Iris cyst. ▪ Anterior subcapsular cataract. **Contraindications:** • Angle closure glaucoma. • Asthma. • Parkinsonism. • It can cause **apnea** if used with succinylcholine or procaine. Be careful in general anesthesia and use atracurium as an alternative.

Cholinergic agonists

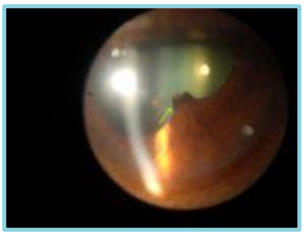
Side-effects:	• **Headache** (contraction of the ciliary muscle will cause spasm). • Cataract, miotic cysts & rarely retinal detachment. (shift of the vitreous behind the iris) **Systemic:** (drug will be absorbed by the lacrimal duct/ vessels/ nasal mucosa > system) • lacrimation, salivation, perspiration, **bronchospasm**, urinary urgency, nausea, vomiting and diarrhea.		➔A patient is presenting to the ER with acute appendicitis, for example, & should be taken immediately to the OR for appendectomy under GA; then you found out that the pt is using phospholine iodide as a topical medication; it is important not to use succinylcholine when inducing anesthesia.

Cholinergic antagonist

Examples:	• **Tropicamide**(4-6h), **cyclopentolate**(12h), homatropine(24h), scopolamine (1-2 days), atropine(2-3 days) (longest DOA). • Manufactured with a red cap bottle.
Mechanisms of action:	• **Mydriasis** (dilation of pupil) by paralyzing the sphincter muscle with **cycloplegia** by paralyzing the ciliary muscle. • Paralysis of ciliary muscle will result in loss of accommodation; thus, you have to warn the patients that they won't be able to read or accommodate for the duration of action of the medication(صروري! يمكن يكون عبده سعلة يحتاج بركبر).
Uses:  Posterior synechia	• Fundoscopy. • Cycloplegic refraction is a procedure to measure the refractive error (glasses prescription). ➔ Refraction; In adults it is usually a straightforward procedure, but children tend to accommodate which will give wrong measurements for refraction. so, we give them cycloplegic medications to stop this accommodation. • Anterior uveitis to avoid posterior synechia (adhesion between the iris and the lens). ➔ We give it to decrease the contact between the iris and the lens→ decrease adhesions). ➔ Cycloplegic drop helps manage pain when there is inflammation in the eye, the ciliary body may spasm, causing pain.
Side-effects:	• local: ○ Allergic reaction. ○ Blurred vision because of dilated pupil especially in bright light

Cholinergic antagonist

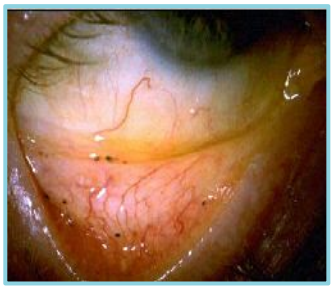
Side-effects:	• Systemic: ○ Nausea & vomiting. ○ Pallor. ○ Vasomotor collapse. ○ Constipation. ○ Urinary retention. ○ Confusion. ★ Specially in children they might cause flushing, fever, tachycardia, or **delirium.** • Treatment by DC (discontinuation) or physostigmine as an antidote



Adrenergic agonists

Adrenergic agonists	Non-selective agonists	Selective agonists	
Examples:	(α1 , α2 , β1 , β2) E.g. epinephrine, dipivefrin (prodrug of epinephrine). Dipivefrin is more potent than epinephrine with less side-effects.	**Alpha-1 agonists** (e.g. **phenylephrine**) work on muscle.	**Alpha-2 agonists** (e.g. brimonidine (Alphagan), apraclonidine) decreases the pressure. - Most common
Uses:	Used in open angle glaucoma. Nowadays is not used commonly	• Used to **induce mydriasis** for fundus evaluation **without cycloplegia** as it does not have effect on the ciliary muscle. - If a patient is dilated & is **still able to read (MCQ)**, most likely was dilated using phenylephrine. • Decongestant (it is a vasoconstrictor).	Glaucoma treatment and prophylaxis against IOP spiking after glaucoma laser procedures. We give it to the patient before the procedure so even when IOP increased will Not be significant. (treatment of the open angle not the closed angle).

Adrenergic agonists

Mechanisms of action:			• Decrease aqueous production. • Increase uveoscleral outflow. ➔ Most of the aqueous drainage happens through the trabecular meshwork (conventional), and less than 10% of total drainage happens through uveoscleral outflow. This medication affects only the **uveoscleral** outflow.
Side-effects:	• Headache. • Arrhythmia. • Increased Blood pressure. • Cystoid macular edema in aphakic eyes (with no lens). ★ Conjunctival adrenochrome (or pigmentation) **(MCQ)**. ★★ 	★ It can cause a significant **increase in blood pressure** can reach stroke level especially in infants & susceptible adults (even with topical administration). ➔ In pts w/ high BP we use the **anti-cholinergic (tropicamide)** drops for dilation. • Rebound congestion (eye become more red with chronic use so should not be used on a regular basis). • Precipitation of acute angle-closure glaucoma in patients with narrow angles. ➔ With pupil dilation, more iris tissue will be crowded at the angle, therefore, the aqueous outflow will decrease & the IOP will increase.	**Local:** • Allergic reaction. • Mydriasis. • Conjunctival blanching (decongestant). • Lid retraction (it activates sympathetic which innervates muller muscle). ➔ In the exam: pic & asking which eye is using α2 agonist? The more opened eye. ➔ Another example: pic with one retracted lid & will ask what sort of medication is this patient using? α2 agonist (brimonidine, apraclonidine) **Systemic:** • Oral dryness. • Headache. • Fatigue. • Drowsiness. • Orthostatic hypotension. • Vasovagal attacks.
Contraindications:	• Closed angle glaucoma. Why? Because of pupil dilation • Cardiac patients.		• Infants → might cause apnea, CNS side effects. • Children below 11 → **respiratory depression** MAO inhibitors (anti psychiatric drugs) users → induce HTN.

Adrenergic antagonists

Adrenergic antagonists	Alpha adrenergic antagonists.	Beta-adrenergic antagonists (beta-blockers)
Examples:	Thymoxamine, Dapiprazole.	**Nonselective**: timolol, levobunolol, metipranolol, carteolol. **Selective:** betaxolol (beta 1 "cardio-selective").
Uses:	• To reverse pupil dilation produced by phenylephrine • **Not widely used.**	Glaucoma (commonly used to treat glaucoma because of their action on reducing the formation of aqueous humour by ciliary body).
Mechanisms of action:		Reduces the formation of aqueous humor by the ciliary body.
Side-effects:		★ **Bronchospasm** (less with betaxolol). ➔ If a patient is having bronchial asthma , we don't use beta blockers for glaucoma; However, when the IOP isn't controlled by other anti-glaucoma medications, we use the cardio-selective. • Cardiac impairment.

Carbonic anhydrase inhibitors

Examples:	**Acetazolamide** (Diamox,oral or IV), methazolamide, dichlorphenamide, dorzolamide (topical), brinzolamide.
Uses:	• Glaucoma (drops,oral) (if not responding to other meds). • Cystoid macular edema. (Drops,Ointment) • Idiopathic intracranial hypertension pseudotumor cerebri. (oral) ➔ Increased ICP without the presence of a tumor, we use the medication to suppress production of aqueous humor and CSF. CSF→↑ICP→ resembling tumor.
Mechanisms of action:	**Aqueous suppression** (carbonic anhydrase has a role in producing aqueous humor).
Side-effects:	• Myopia. ★ **Paresthesia** (circumoral numbness and peripheral numbness). • Anorexia. • GI upset. • Headache. • Altered taste and smell. • Na and K depletion, metabolic acidosis with normal anion gap. • Renal stone. • Bone marrow suppression "aplastic anemia" (can be caused even with one dose aka idiosyncratic effect).
Contraindications:	• Sulfa allergy as it is a sulfa derivative. • Digitalis users (pts lose K when using digitalis along with K loss from carbonic anhydrase inhibitor) → lethal hypokalemia. • Pregnancy.- teratogenic "category C medication " • Renal stones

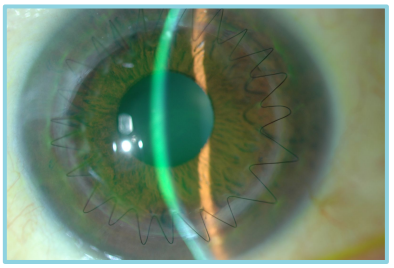
Osmotic agents

- **Dehydrate** vitreous body which reduces IOP significantly in acute attacks.
  ➔ Loading the circulation with a concentrated fluid → water will move from less concentrated (vitreous) to more concentrated (circulation). we are basically dehydrating the vitreous resulting in a significant decrease in IOP.
  ➔ In cases of a sudden increase in IOP, patients become symptomatic (present w/ pain, headache, nausea & vomiting).
- Examples are:
  - ★ Glycerol 50% syrup (oral) that can cause nausea & **hyperglycemia** (caution in uncontrolled DM).
  - ★ Mannitol 20% IV **causes fluid overload & is not used in heart failure** and renal impairment! (evaluate CVS before use).
    - It is used in case of acute angle closure glaucoma to reduce IOP rapidly.

Prostaglandin analogue	
Examples:	latanoprost, bimatoprost, travoprost, unoprostone.
Uses:	Glaucoma. **First line for Glaucoma** (used a lot once a day) ➔ A patient who has bronchial asthma and high blood pressure presented with open angle glaucoma. the most appropriate drug to treat glaucoma? prostaglandins analogue.
Mechanisms of action:	Increases **uveoscleral** aqueous outflow (same as alpha-2 adrenergic agonists).
Side-effects:	★ Darkening of the iris with chronic use .especially when using it unilaterally causing **(heterochromia iridis).** • Lengthening and thickening of eyelashes. • Intraocular inflammation because it's an inflammatory mediator. • Macular edema.because it's an inflammatory mediator.

Finding: heterochromia iridis (of the left eye). Name one medication that can cause it? **Prostaglandin analogue e.x: latanoprost**

Anti-inflammatory

	Corticosteroids more potent		NSAIDS Less anti-inflammatory effect, but less side effects.
	Topical	**Systemic**	
Examples:	• Fluorometholone. • Remixolone. • Prednisolone. • Dexamethasone • Hydrocortisone.	• Prednisolone. • Cortisone.	• Ketorolac (Acular/Acuvail). • Diclofenac. • Flurbiprofen
Uses:	• Post-operatively (to reduce inflammation) • Anterior uveitis. • Severe allergic conjunctivitis. -We don't use it as 1st line, only if other medications failed, and only for a short period of time. • Vernal keratoconjunctivitis -A severe form of ocular allergy. • Prevention & suppression of corneal graft rejection. • Episcleritis. • Scleritis.  This patient underwent corneal transplant.	• Posterior uveitis. -Where topical medication doesn't reach in therapeutic concentrations • Optic neuritis. • Temporal arteritis with anterior ischemic optic neuropathy (optic disc swelling). -Typical scenario: an old man (70+) presenting with a sudden painful decrease of vision. -We use the medication not to regain the vision in the effected eye, but to protect the other eye and other organs.	• Post-operatively → ↓inflammation. • Mild allergic conjunctivitis. ★ Episcleritis.(main use) • Mild uveitis. • Cystoid macular edema.(post op) • Preoperatively to prevent miosis during surgery to inhibit prostaglandin → dilation. We want them dilated during surgery • Added with steroids
Mechanisms of action:	Inhibition of arachidonic acid release from phospholipids by inhibiting phospholipase A2 (very potent).		Inactivation of cyclooxygenase enzyme which is responsible for the production of the PG, prostacyclin and thromboxane (prevent formation of PG which causes miosis, so we use it in cataract surgery)

Anti-inflammatory

Side-effects:

- Susceptibility to infections (especially fungal infections) because it decreases immunity
- ★ **Glaucoma** because with chronic use of the medication the pressure will build up gradually (asymptomatic) leading to glaucoma and optic nerve damage which is irreversible. ★★
- Cataract. more w/ systemic
- Ptosis.
- Mydriasis.
- Scleral melting.
- Skin atrophy.

- The most serious side-effect of topical steroids is increased IOP (steroid-induced glaucoma) that is asymptomatic permanent damage. It causes glaucoma more than cataract
- Remember that it does NOT cause optic neuritis.

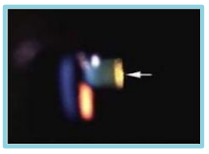
Local:

★ **Posterior subcapsular cataract.**

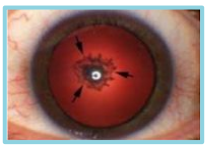
- Glaucoma. But causes cataract more (important)
- Central serous retinopathy

Systemic:

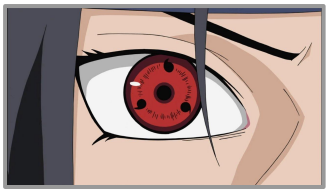
- **Suppression of pituitary adrenal axis** do NOT stop it abruptly, taper the dose gradually.
- Hyperglycemia,
- Osteoporosis
- Peptic ulcer
- Psychosis.



Posterior subscapular cataract "slit lamp"



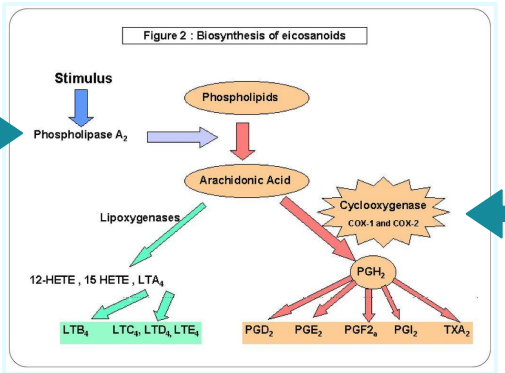
Posterior subscapular cataract "retroillumination"



الاكاديمك موصي

Stinging. (Irritation)

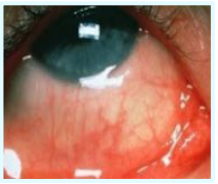
Corticosteroids inhibit phospholipase A2 " up in the cascade " → more potent .

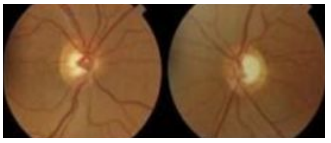


NSAIDs inactivate cyclooxygenase " affect only one limb of the inflammatory pathway → less potent .

Anti-allergic

- Remember: the use of antiallergic (antihistamines or steroids) should be temporary (only prescribed in serious situations and for a short period because of the serious side effects).
- Avoidance of allergens (best treatment), cold compressors & lubricants (without preservatives).



Types	Examples	Mechanisms and Uses	Side-Effects
Antihistamines	• Pheniramine. • Levocabastine.	Work by blocking histamine that is produced by the body in response to allergens or irritants.	• Drowsiness. • Bradycardia. • 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. • 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.	It is used in mild allergic conjunctivitis.	Stevens Johnson syndrome
Corticosteroids	• Fluorometholone. • Remixolone. • Prednisolone.	• If the symptoms could not be controlled by the previous medications, then use topical steroids for instant relief. • You need to instruct the patient that this medication shouldn't be used without a follow up because it may increase the IOP without any symptoms resulting in glaucoma "irreversible optic nerve damage " and fungal infections. 	• Posterior subcapsular cataract. • Glaucoma. • Papilledema. • Predisposition

Drug combination (if needed).

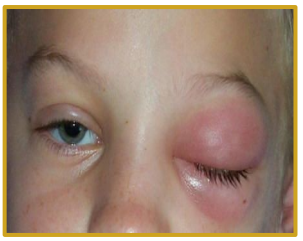
Antibiotics

Examples	Penicillins, Tetracyclines, Fluoroquinolones, Cephalosporins, Chloramphenicol, Vancomycin(commonly used)+Ofloxacin, Sulfonamides, Aminoglycosides, Macrolides.

Uses

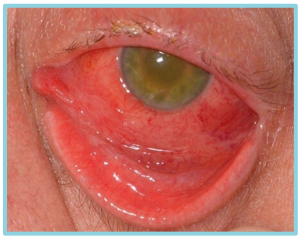
- Used topically in prophylaxis (pre and postoperatively) and treatment of ocular bacterial infections.

★ Used **orally for the treatment of pre-septal cellulitis** (inflammation of the subcutaneous tissue in front of the orbital septum & it can be treated more easily than orbital cellulitis).
  - Patients present with swelling of the lid.
  - e.g. **amoxicillin with clavulanate** (Augmentin), cefaclor.



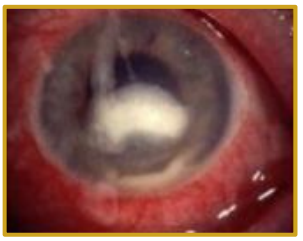
Pre-septal cellulitis
Treatment: oral antibiotics & warm compressors.

★ Used **intravenously for the treatment of orbital cellulitis** (inflammation or infection behind the orbital septum).
  - A true ophthalmic emergency that can progress, if untreated, to meningitis, encephalitis, cavernous sinus thrombosis or sub-periosteal abscess, that's why we have to admit the patients & treat them aggressively with IV antibiotics).
  - Patients usually have fever, a history of sinusitis & present with proptosis (protrusion of the eye) & limited extra-ocular motility.
  - e.g. gentamicin, cephalosporin, vancomycin, flagyl.



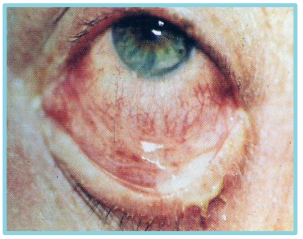
Endophthalmitis

★ Can be **injected intravitreally vancomycin for the treatment of endophthalmitis.**
  - Endophthalmitis can be caused by trauma or surgery.
  - Classical scenario: a patient underwent a cataract surgery, the pt was doing well in the 1st day; on the 2nd day, the pt developed decrease in vision, pain & redness. On exam, there are lid swelling, conjunctiva is red & edematous (chemosis) & hypopyon.



Abnormalities: hypopyon & corneal opacity.
Complication: corneal ulcer.

- Trachoma can be treated by topical and systemic tetracycline, erythromycin or systemic azithromycin (caused by chlamydia trachomatis).
- Bacterial keratitis (bacterial corneal ulcers) can be treated by <u>topical fortified</u> (concentrated antibiotics) penicillins, cephalosporins (ceftazidime), aminoglycosides, vancomycin, or fluoroquinolones "hourly" (high duration and frequency)
  - Keratitis means inflammation of the cornea.
  - There is a difference between corneal ulcer & abrasion, which is the discontinuation of the epithelial tissue. However, when it gets infected along w/ some degradation of the stromal tissue then we call it corneal ulcer. The cornea which is normally transparent becomes opacified because the infection affects the stroma, the problem is that cornea will end up with a permanent scar.



Mucopurulent discharge

- Bacterial conjunctivitis "manifested by conjunctival redness and frequent discharge" is usually self-limited but topical erythromycin, aminoglycosides, fluoroquinolones, or chloramphenicol can be used (to speed it up, we use broad-spectrum Abx). .

Antifungal

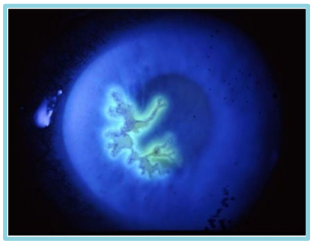
Uses:	Fungal keratitis, fungal endophthalmitis.

Polyenes	• E.g. amphotericin B (commonly used one), natamycin.
	  ○ Damage cell membrane of susceptible fungi.
	  ○ Side-effects: **nephrotoxicity**

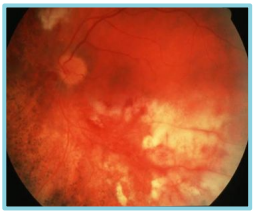
Imidazoles	• E.g. miconazole, ketoconazole. ○ Increase fungal cell membrane permeability.
Flucytosine	Act by inhibiting DNA synthesis of the fungi .

Antiviral

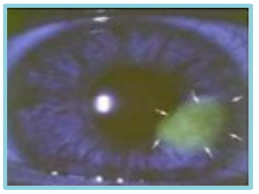
Acyclovir	• Interact with viral thymidine kinase (selective). • Used in herpetic keratitis. • Topically (ointment) or IV - We put a fluorescein dye into the eye it collects in areas with no epithelium; And when we view it with a blue light, these areas become green. If the areas (abrasions) appear in a dendritic (branching) fashion, then most likely it is herpetic keratitis, especially if it's associated with a decreased corneal sensation.
Trifluridine	• We use it if there is uveitis associated with keratitis. • Because it has more corneal penetration. • Can treat herpetic iritis.
Ganciclovir	Used intravenously (or intravitreal) for CMV "cytomegalovirus" Retinitis. - Pic : whitish patches " infiltrate due to CMV retinitis " .



Stained eye showing dendritic shape ulcer, most likely herpetic keratitis in fluorescein stain.

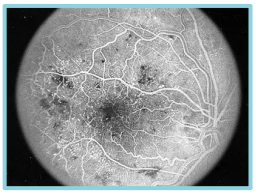


Ocular diagnostic drugs

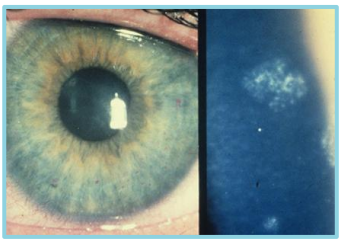


Fluorescein dye: **(Most common one)**

- 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 (NLD obstruction).
    - To diagnose NLD obstruction, we put fluorescein in both eyes, then we view the eyes after 5 minutes, the eye that has less concentration of fluorescein is the normal eye and the one with higher concentration has lacrimal duct obstruction. This happens because the patency of the duct is affected & less amount of dye will go to the nasal cavity.
  - Fluorescein angiography (fluorescein is injected I.V. → goes to the circulation → retinal circulation to delineate the retinal vasculature; it can also show any pathology or leakage in the fundus).



- Caution!
  - ★ **Stains soft contact lens,** so before staining ask if the patient is wearing any contact lens as fluorescein might stain it permanently.
  - Fluorescein drops can be contaminated by pseudomonas sp (used to happen in the past not anymore) because now we use single use drops.



Dendritic staining with fluorescein

Rose Bengal Stain: (not used anymore)

- Stains devitalized (dead) epithelium.
- Uses:
  - Severe dry eye
  - Herpetic keratitis

Local anesthesia

Topical:

- E.g. proparacaine, tetracaine or Benoxinate
  - Uses: (when you want to deal with cornea)
    - Applanation tonometry to stop corneal reflex.
    - Gonioscopy to view 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 If used chronically it will cause delayed healing .
    - Allergic reaction rarely.

Orbital infiltration:

- Peribulbar (around the globe) or retrobulbar (behind the globe).
  - Cause anesthesia (pt isn't able to feel) and akinesia (pt isn't able to move the eyes) for intraocular surgery.
  - E.g. lidocaine, bupivacaine.
  - Can cause temporary vision loss, diplopia.

Other Ocular Preparations

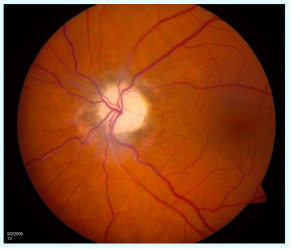
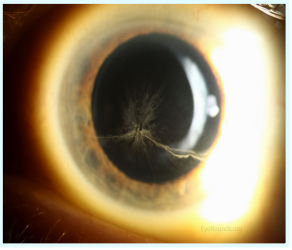
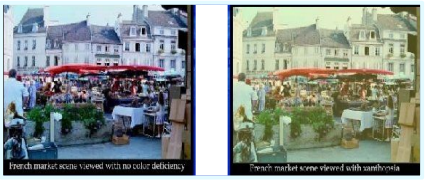
Lubricants

- Drops or ointments. (Depends on severity of dryness)
- Polyvinyl alcohol, cellulose, methylcellulose.
- Preserved or preservative free (less irritation) good for px with allergy. If the dryness is mild you can use it with preservative with lower frequency but if dryness is severe then higher frequency without preservative. If it is extremely dry then go for gel or ointments.

Ocular toxicology

Complications of topical administration:

- Mechanical injury from the bottle e.g. corneal abrasion. Especially in older pts with hand problems such as RA or tremor
- ★ Pigmentation: epinephrine adrenochrome. MCQ!!!!!! ★★
- Ocular damage: e.g. topical anesthetics, benzalkonium(preservatives)
- Hypersensitivity: e.g. atropine(causes delirium in childrens), neomycin, gentamicin. Highly irritant to the eyes
- Systemic effect: topical phenylephrine can increase BP. (Use tropicamide instead)
- Use prostaglandins instead of timolol in asthmatic patients

Drug	Effect
Amiodarone	• A cardiac arrhythmia drug. ★ **Causes optic neuropathy*** (mild decreased vision, visual field defects, bilateral optic disc swelling). - If a patient develops optic neuropathy, the amiodarone has to be discontinued. ★ Also causes **corneal vortex keratopathy (corneal verticillata)*** white streaks on the cornea which is whorl-shaped pigmented deposits in the corneal epithelium. -corneal verticillata does not cause any visual significance and it's reversible . *Important for MCQ!!!!!!  Pale optic nerve  corneal verticillata
Digitalis	• A cardiac-failure drug. ★ Causes **chromatopsia (objects appear yellow)** with overdose (causes optic neuropathy (abnormal perception of color, 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 & pepper retina

Diphenylhydantoin 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.

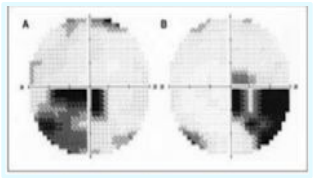
Ocular toxicology

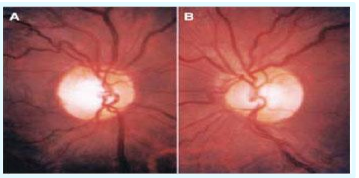
Topiramate

- A drug for epilepsy.
- Causes acute angle-closure glaucoma (acute eye pain, headache, nausea, vomiting, 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 (we have to use another anti-epileptic medication).

Ethambutol

- An anti-TB drug. (**Isoniazid** can cause optic neuropathy as well)
- Causes a dose-related optic neuropathy.
- Usually reversible but occasionally permanent visual damage might occur. Visual field should be tested

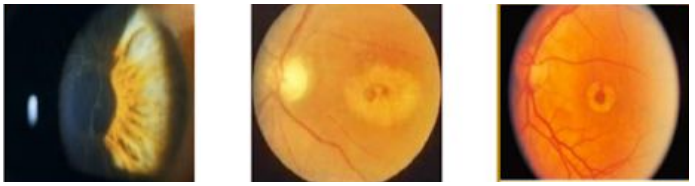




The function of the optic nerve is reflected by the visual field test

Chloroquine

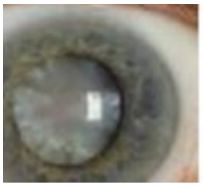
- E.g. chloroquine, hydroxychloroquine.
- Used in malaria, rheumatoid arthritis, SLE.
- ★ Cause **vortex keratopathy (corneal verticillata)** which is usually asymptomatic but can present with glare and photophobia.
- ★ Also cause **retinopathy** (bull's eye maculopathy) with accumulative dose .
  - Chronic users more than 3 years.
  - That's why any patient on chloroquine should be followed routinely in ophthalmology clinic to detect early changes as they reversible but later changes are NOT
- Vortex keratopathy could be caused by BOTH amiodarone and chloroquine.



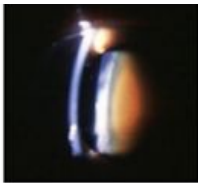
Diagnosis: bull's eye maculopathy. What medication can cause it: chloroquine

HMG-CoA REDUCTASE INHIBITORS (STATINS):

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



Mature cataract on diffused illumination



"Slit lamp" yellowish discoloration of the lens → cataract .

Ocular toxicology

Other Agents	
Methanol	**Optic atrophy** and blindness (patient presents with history of alcohol drinking).
Contraceptive pills	**Pseudotumor cerebri** now called " idiopathic or benign intracranial hypertension **(papilledema)**, and dryness (manifested by contact lens intolerance). Vascular occlusion Bilateral optic disk swelling
Chloramphenicol and streptomycin	Optic atrophy. Optic neuropathy!
Hypervitaminosis A ★★	Increased ingestion of vitamin A causes yellow skin and conjunctiva, **pseudotumor cerebri (papilledema)** & retinal hemorrhage. (Isoprenoid meds)
Hypovitaminosis A ★★	Malnutrition (↓consumption of vitamin A) → **night blindness (nyctalopia),** keratomalacia (melting of the cornea). Most common cause of night blindness is retinitis pigmentosa.

Agents that can cause toxic optic neuropathy:

- ★ Methanol (patient consumes alcohol that is made improperly> can cause irreversible blindness).
- **Ethylene glycol (antifreeze).**
- ★ Chloramphenicol.
- ★ Isoniazid.
- 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) in a high-protein diet
- Radiation unshielded (exposure to >3,000 rads).

Question from Dr. Abdullah : what are the agents that can cause optic neuropathy ? Highlighted in red

Lecture Quiz

Q1-A 60-year-old glaucoma patient was prescribed a medication for increased intraocular pressure. She developed peripheral and circumoral paresthesia. Her complete blood count showed severe anemia, Which of the following drugs was prescribed?

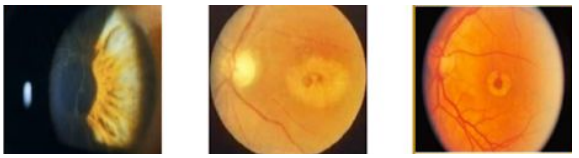
A. Glycerol
B. Acetazolamide
C. Mannitol
D. Beta-blockers

Q2- Child with flushing, fever, tachycardia, and delirium, which medicine did he take?

A. Atropine
B. Physostigmine
C. Digitalis
D. Timolol

Q3-A 44 year old female known case of SLE 6 years ago and she is on hydroxychloroquine, examination of the eye showed the following, what is the diagnosis?

A. Posterior subcapsular cataract
B. Salt and pepper retina
C. Conjunctival adrenochrome
D. bull's eye maculopathy



Q4- A 54 year old man newly diagnosed to have glaucoma. He is known case of asthma and taking regular inhalers. Which agent would you try to avoid when prescribing him glaucoma medication?

A. Acetazolamide
B. Timolol
C. Dorzolamide
D. Latanoprost

Q5-Hypervitaminosis A can cause all of the following except?

A. Yellow conjunctiva
B. Papilledema
C. Retinal hemorrhage
D. Night blindness

Answers: Q1: B | Q2: A | Q3: D | Q4: B | Q5: D

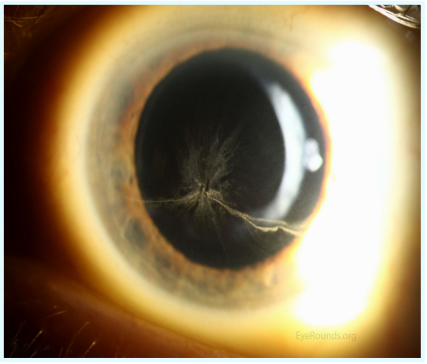
Short Answer Questions

Case 1

A:What is the abnormal finding?

B:Name 1 drug can cause this?

Case 2



A:What is the abnormal finding?

B:Name 2 drugs can cause this?

Answers:
Case 1
A: heterochromia iridis
B: Prostaglandin analogous (latanoprost)

Case 2
A: vortex keratopathy (corneal verticillata)
B: 1. Amiodarone 2.Chloroquine

This work was originally done by **438 and 439 Ophthalmology Team**

Edited by **441 Ophthalmology Team**

Team leaders:

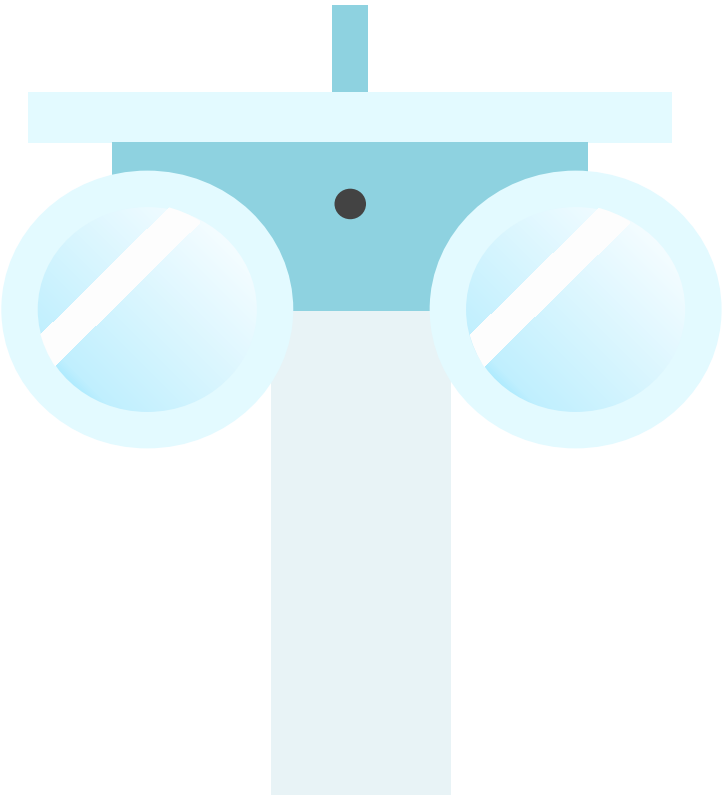
Abdullah Aldayel **Ibrahim Aljurayyan** **Sultan Alosaimi**

Members:

Abdullah Aldayel

Note Takers:

Ibrahim Aljurayyan **Mohammed alsaqabi**



441 Ophthalmology Team

A **HUGE** thanks to all whom worked day and night to bring out this amazing teamwork

Team leaders:

Abdullah Aldayel Ibrahim Aljurayyan Sultan Alosaimi

Members & Note Takers:

Abdulaziz Alabdulrahman
Abdulaziz Alqusiyer
Abdulaziz Annab
Abdullah AlQarni
Abdulrahman Badghaish
Bassam Ahmed
Faisal AlRashed
Faisal Alsaawi
Hamad Alkhenizan
Hamad Alshaalan
Mansor aldaijy
Mohammed Alfaris
Mohamed AlQahtani
Mohammed alsaqabi
Nawaf Alghamdi
Nawaf alsanea