433 Teams

OPHTHALMOLOGY

Ocular Pharmacology
&
Toxicology

Color index:

432 Team – **Important** – **433 Notes** – **Not important**

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1- Ocular pharmacology…

- Cholinergic agonist
- Cholinergic antagonist
- Adrenergics agonist
- Adrenergics antagonist
- Prostaglandin agonist
- Local anesthetics
- Ocular diagnostic drugs
- Osmotic agents
- Carbonic anhidrase
- Anti-inflammatory (Steroids, NSAID, anti-allergics)
- Anti-Microbial (Atni-biotics, Anti-viral, Anti-fungal)

2- Ocular toxicology…

Pharmacodynamics:

*It is the biological and therapeutic effect of the drug (mechanism of action).
*Most drugs act by binding to regulatory macromolecules, usually neurotransmitters or hormone receptors or enzymes.
*If the drug is working at the receptor level, it can be agonist or antagonist.
*If the drug is working at the enzyme level, it can be activator or inhibitor.

Pharmacokinetics:

*It is the absorption, distribution, metabolism, and excretion of the drug.
*A drug can be delivered to ocular tissue as:

-Locally: (Eye drop, Ointment, Periocular injection (if we want to bypass the surface epithelium and give high concentration of drug behind the ant. Part of eye: vitreous is avascular structure and good media for infection, so we give antibiotic through this technique), Intraocular injection)
-Systemically: (Orally, IV.)

Factors influencing local drug penetration into ocular tissue: (Memorize it):

***Drug concentration and solubility:** the higher the concentration the better the penetration e.g pilocarpine 1-4% but limited by reflex tearing. (but put in mind if the concentration exceeds 4%, the more tearing reflex, the drug effects washed out.)cornea and conjunctiva are sensitive, with increasing the concentration it may cause irritation > protecting lacrimation > dilute the medication

***Viscosity:** addition of methylcellulose and polyvinyl alcohol increases drug penetration by increasing the contact time with the cornea and altering corneal epithelium Some of the drugs with high viscosity increase the epithelial damage in case of present epithelial pathology or decrease its healing or may cause the damage itself

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

***Surfactants:** the preservatives used in ocular preparations alter cell membrane in the cornea and increase drug permeability e.g. benzylkonium and thiomersal

*__PH:__ the normal tear pH is 7.4 and ifthe drug pH is much different, this will cause reflex tearing.

*__Drug tonicity:__ when an alkaloid drug is put in relatively alkaloid medium, the proportion of the uncharged(non-ionic) form will increase, thus more penetration. (non-ionic is the most effective form of the drug)

Eye drops:

* Eye drops- most common
* one drop = 50 µl
* Volume of conjunctival cul-de-sac 7-10 µl
* Measures to increase drop absorption:
  -Wait 5-10 minutes between drops.
  - compress lacrimal sac and keep the eye closed (To avoid drops escape through NasoLacrimal Duct) which could cause systemic side effects.
  -keep lids closed for 5 minutes after instillation -keep lids closed for 5 minutes after instillation.

Ointments:

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

Peri-ocular injections:

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

Intraocular injections

* Intracameral (within anterior chamber) or intravitreal
* E.g. – Intracameral acetylcholine (miochol) :
During cataract surgery
– Intravitreal antibiotics in cases of endophthalmitis (inflammation that reaches viterous chamber) topical can't reach vitrous.
– Intravitreal steroid in macular edema – Intravitreal Anti-VEGF for DR. (Diabetic Retinopathy)
– Duration won't exceed 72 h in vitreous

Sustained-release devices:

* These are devices that deliver an adequate supply of medication at a steady-state level (like glaucomatous patients)
* E.g. – Ocusert delivering pilocarpine – Timoptic XE delivering timolol – Ganciclovir sustainedrelease intraocular device – Collagen shields. (Contact lenses filled with medication)

Systemic drugs:

* Oral or IV (IV only if sever infection or there is GI disturbance for ex.)
* 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 of degeneration of blood ocular barrier)

Ocular pharmacology

Cholinergic agonists:

Directly acting agonists:	Indirectly acting (anticholinesterases): *More potent with longer duration of action*	
E.g. pilocarpine, acetylcholine (miochol), carbachol (miostat)	**Reversible inhibitors**	Irreversible
Uses: To Induce miosis, for glaucoma	e.g. physostigmine used in the diagnosis of Myasthenia Gravis	e.g. phospholine iodide
Mechanisms: * Miosis by contraction of the iris sphincter muscle. * increases aqueous outflow (inside eye to outside) through the trabecular meshwork by longitudinal ciliary muscle contraction. * Accommodation by circular ciliary muscle contraction.	**Used**: in glaucoma (rarely) and lice infestation of lashes. (because it make the eyelashes fall down)	**Uses:** in accommodative esotropia (they have strabismus when focusing in typically farsightedness)
Side effects: *Local: diminished vision (myopia with long use), headache (ciliary muscle spasm), cataract, miotic cysts, and rarely retinal detachment(it may happen if using dilating drops and after you want to revers it with constricting drops in predisposed individuals) (Because it contracts the iris, can pull peripheral retina, results in detach.) * systemic side effects: lacrimation, salivation, perspiration, bronchial spasm, urinary urgency, nausea, vomiting, and diarrhea	**Side effects:** can cause CNS side effects.	**Side effects:** Iris cyst and anterior subcapsular cataract. (differs from steroids induce cataract!) **Contraindicated :** in angle closure glaucoma, asthma, Parkinsonism -causes apnea if used with succinylcholine or procaine

Cholinergic Antagonists:

E.g. tropicamide, cyclopentolate, homatropine, scopolamine, atropine (stays for 2 weeks)

* Cause mydriasis (by paralyzing the sphincter muscle) with cycloplegia (by paralyzing the ciliary muscle,so there is loss of accommodation

Uses: fundoscopy, cycloplegic refraction (procedure to measure accommodation) ,anterior uveitis (because it's attenuate endotoxin induced uveitis)

*** Side effects**:

– local: allergic reaction, blurred vision

– Systemic: nausea, vomiting, pallor, vasomotor collapse, constipation, urinary retention, and confusion

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

***Treatment** by discontinuation or physostigmine.

Carbonic Anhydrase Inhibitors

(carbonic anhydrase have a role in producing aqeous humor)

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

* **Uses**: glaucoma, cystoid macular edema, pseudotumour cerebri

* **Mechanism**: aqueous suppression

* **Side effects**:

myopia, paresthesia (in extremities) , anorexia, GI upset, headache, altered taste and smell(decreases CSF production), Na and K depletion, metabolic acidosis, renal stone, bone marrow suppression "aplastic anemia"

* **Contraindication:**

sulpha allergy, digitalis users(hypokalemia), pregnancy.

Adrenergic Agonists: (be careful for: cardiac disease, asthma and BP)

Non-selective agonists (α1, α2, β1, β2)	Alpha-1 agonists	Alpha-2 agonists: *Mechanism: decrease aqueous production, and increase uveoscleral outflow*
E.g. epinephrine, depevefrin (pro-drug of epinephrine)	E.g. phenylepherine	E.g. brimonidine, apraclonidine
Uses: Glaucoma (no more used to treat it)	**Uses**: mydriasis (without cycloplegia), decongestant	**Uses:** glaucoma treatment (treatment of the open angel not the closure angle), prophylaxis against IOP spiking after glaucoma laser Procedures
Side effects: arrhythmia, increased blood pressure, Conjunctival adrenochrome (it's reminant of the depevefrin) , cystoid macular edema in aphakic (No lens) eyes trauma or surgical cataract removal, so accommodation lost expected hypermetropia. **–Contraindicated:** in closed angle glaucoma	**Side effects**: Can cause significant increase in blood specially in infant and susceptible adults – Rebound congestion not indicated in regular use) – precipitation of acute angle-closure glaucoma patients with narrow Angles	**Side effects:** **local:** allergic reaction, mydriasis, lid retraction,(stimulation of molar muscle that supplied by sympathetic NS) conjunctival blanching **systemic:** oral dryness, headache, fatigue, drowsiness, orthostatic hypotension, vasovagal attacks **Contraindications:** infants, MAO inhibitors users

Adrenergic Antagonists:

Alpha adrenergic antagonists	Beta-adrenergic blockers 1st line of Glucoma treatment *Mechanism: reduce the formation of aqueous humor by the ciliary body*
E.g. thymoxamine, dapiprazole	E.g. – non-selective: timolol (commonly used to treat glaucoma), levobunolol, metipranolol, 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 (by suppressing aqueous production)
	Side effects: bronchospasm (less with betaxolol), (non-selective:exacerbates bronchial asthma, COPD)cardiac impairment.

Osmotic Agents (used to supress IOP as fast as possible in Acute attacks)

* Dehydrate vitreous body which reduce IOP significantly
* E.G.
  – glycerol 50% syrup (cause nausea, hyperglycemia)
  – Mannitol 20% IV (cause fluid overload and not used in heart failure)(screen CVS before use)

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 (it's inflammatory mediator so better avoid it in inflammation), macular edema.

Anti-Inflammatory: The 3rd category: steroid sparing agent.

Corticosteroids – *Mechanism: inhibition of arachidonic acid release from phospholipids by inhibiting phosphlipase A2*		NSAID *Mechanism: inactivation of cyclooxygenase*	Anti-allergics
Topical – E.g. fluorometholone, remixolone (weakest) , prednisolone, hydrocortisone (both are the strongest), dexamethasone.	**Systemic**: – E.g. prednisolone, cortisone	E.g. ketorolac, diclofenac, flurbiprofen	* Avoidance of allergens, cold compress, lubrications. *Antihistamines (pheniramine, levocabastine) *Decongestants (naphazoline, phenylepherine, tetrahydrozaline- not preferable as it causes rebound congestion) *Mast cell stabilizers takes few days to start induce action. (cromolyn, lodoxamide, pemirolast, nedocromil, olopatadine = the
Uses: postoperatively, anterior uveitis, severe(not mild or modeate) allergic conjunctivitis – they suffer a lot because when we give steroids they feel better so they used it a lot but at the end they develop glaucoma, cataract. , vernal keratoconjunctivitis, prevention and suppression of corneal graft rejection, episcleritis, scleritis.	**Uses**: posterior uveitis, optic neuritis, temporal arteritis with anterior ischemic optic neuropathy	**Uses**: postoperatively, mild allergic conjunctivitis, episcleritis, mild uveitis, cystoid macular edema, preoperatively to prevent miosis during surgery (Surgical trauma induce miosis due to PG release, that's why we use NSAID)	

Side effects: susceptibility to infections (especially fungal) , glaucoma, cataract(mostly in topical), ptosis, mydriasis, scleral melting, skin atrophy In topical steroids it is likely to induce glaucoma but less likely cataract in comparison, while the systemic steroids do induce cataract but it can induce glaucoma as well.	**Side effects:** Local: posterior subcapsular cataract(mostl y in systemic), glaucoma, central serous retinopathy Systemic: suppression of pituitary- adrenal axis(so, reduce dose to allow intra production), hyperglycemia, osteoporosis, peptic ulcer, psychosis	**Side effects:** stinging	* NSAID (ketorolac) *Steroids(if other treatments failed)(fluoromet holone, remixolone, prednisolone)(per ipheral vision loss in chronic use) * Drug combinations. Try to mix and let the steroids your least option.

Anti-Microbial:

Antibiotics	Antifungals	Antivirals
Penicillins, Cephalosporins, Sulfonamides, Tetracyclines, Chloramphenicol, Aminoglycosides , Fluoroquinolones, Vancomycin, macrolides	**Uses**: fungal keratitis, fungal endophthalmitis	*Acyclovir interact with viral thymidine kinase (selective) used in herpetic keratitis *Trifluridine more corneal penetration can treat herpetic iritis(the best in uveitis) * Ganciclovir used intravenously for CMV retinitis
*Used **topically** in prophylaxis (pre and postoperatively) and treatment of ocular bacterial infections. * Used **orally** for the treatment of preseptal cellulitis e.g. amoxycillin with clavulonate, cefaclor	*Polyenes – damage cell membrane of susceptible fungi – e.g. amphotericin B, natamycin – **Side effect**: nephrotoxicity *Imidazoles – increase fungal cell membrane permeability – e.g. miconazole, *ketoconazole Flucytocine – act by inhibiting DNA synthesis.	
*Used **intravenously** for the treatment of orbital cellulitis e.g. gentamicin, cephalosporin, vancomycin, flagyl *Can be injected **intravitrally** for the treatment of endophthalmitis with vancomycin and septazidine.	Usually we don't diagnose fungal infection easily, so we treat it as antibacterial if no improvement we add anti fungal. And we take swab from cornea and culture it, and we change antibacterial accordingly.	

*__Trachoma__ (contagious bacterial infection of inner surface of lid) can be treated by topical and systemic tetracycline or erythromycin, or systemic azithromycin. ***Bacterial keratitis** (bacterial corneal ulcers) can be treated by topical fortified penicillins, cephalosporins, aminoglycosides, vancomycin, or fluoroquinolones. *__Bacterial conjunctivitis__ is usually self limited but topical erythromycin, aminoglycosides, fluoroquinolones, or chloramphenicol can be used		

(you have to be aggressive with treatment of pre-septal cellulitis > to avoid complications)

Ocular Diagnostic Drugs:

Fluorescein dye – Available as drops or strips **(The fluorescein is hydrophilic so any damaged structure without epithelium will be dyed with it)**	**Rose bengal stain** Stains devitalized (diseaesed)epithelium
– Uses: stain corneal abrasions, applanation tonometry, detecting wound leak, NLD obstruction, fluorescein angiography.	– Uses: severe dry eye, herpetic keratitis
***stains soft contact lens** * Fluorescein drops can be contaminated by Pseudomonas sp.	

Local Anesthetics:

Topical E.g. **propacaine, tetracaine (acts longer).**	Orbital infiltration: **– peribulbar or retrobulbar(not used any more)**
Uses: applanation tonometry, goniscopy, removal of corneal foreign bodies, removal of sutures, examination of patients who cannot open eyes because of pain.	– cause anesthesia and akinesia for intraocular surgery – e.g. lidocaine, bupivacaine
Adverse effects: toxic to corneal epithelium (if diseased so used when it's needed only), allergic reaction rarely.	

Other Ocular Preparations:

Lubricants: (use it if needed only because it inhibit the reflex tearing and with time inhibiting the nasal secretion if not the main lacrimal)

– drops or ointments

– Polyvinyl alcohol, cellulose, methylcellulose

– Preserved or preservative free.

Intraviteal injection:

* **Anti-VEGF** (vascular endothelial growth factor):

– Bevacizumab (Avastin), Ranibizumab (Lucentis), Aflibercept (Eylea)

***Uses**:

– PDR (proliferative diabetic retinopathy) , DME (Diabetic macular edema) – CRVO(central retinal venous occlusion) , BRVO (Branched retinal venous occlusion) – Wet AMD (agerelated macular degeneration).

Ocular toxicology

Complications of topical administration:

* Mechanical injury from the bottle e.g. corneal abrasion

* Pigmentation: epinephrine adrenochrome

* Ocular damage: e.g. topical anesthetics, benzylkonium

* Hypersensitivity: e.g. atropine, neomycin, gentamicin

* Systemic effect: topical phenylephrine can increase BP.

Amiodarone (no significant effect)

*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 not reversible (objects appear yellow) with overdose.

Chloroquines: no significant effect.

*E.g. chloroquine, hydroxychloroquine

*Used in malaria, rheumatoid arthritis, SLE

*Cause vortex keratopathy (corneal verticillata) which is usually asymptomatic but can present with glare and photophobia

*Also cause retinopathy (bull's eye maculopathy)

Chorpromazine:

*A psychiatric drug

*Causes corneal punctate epithelial opacities, lens surface opacities

*Rarely symptomatic

*Reversible with drug discontinuation.

Thioridazine:

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

Diphenylhydantoin:

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

Topiramate:

*A drug for epilepsy(if the patient came with glaucoma ask if he is epileptic)also usually come with same side headache)
*Causes acute angle-closure glaucoma (acute eye pain, redness, blurred vision, haloes).(moves iris lensediaphragm more anteriorly, block anterior angle, no drainage , in this case we treat by atropine and cyclopentolate , the result will be dilatation ,so it'll pull lense backword.
*Treatment of this type of acute angleclosure glaucoma is by: cycloplegia and topical steroids (rather than iridectomy) with the discontinuation of the drug.

Ethambutol:

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

Agents that Can Cause Toxic Optic Neuropathy:

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

HMG-CoA reductase inhibitors (statins):

*Cholesterol lowering agents
E.g. pravastatin, lovastatin, simvastatin, fluvastatin, atorvastatin, rosuvastatin
*Can cause cataract in high dosages specially if used with erythromycin

Other agents:

*methanol – optic atrophy and blindness
*Contraceptive pills – pseudotumor cerebri (papilledema), and dryness (CL intolerance)
*Chloramphenicol and streptomycin – optic atrophy
*Hypervitaminosis A – yellow skin and conjunctiva, pseudotumor cerebri (papilledema), retinal hemorrhage.
*Hypovitaminosis A – night blindness (nyctalopia), keratomalacia.

This is a useful piece of extra-information that we would like to add:

* Preseptal cellulitis (or periorbital cellulitis) is an infection of the anterior portion of the eyelid, not involving the orbit or other ocular structures. In contrast, orbital cellulitis is an infection involving the contents of the orbit (fat and ocular muscles). Neither infection involves the globe.
* Although preseptal and orbital cellulitis may be confused with one another because both can cause ocular pain and eyelid swelling and erythema, they have very different clinical implications.
* Preseptal cellulitis is generally a mild condition that rarely leads to serious complications, whereas orbital cellulitis may cause loss of vision and even loss of life. Orbital cellulitis can usually be distinguished from preseptal cellulitis by its clinical features (ophthalmoplegia, pain with eye movements, and proptosis) and by imaging studies. In cases in which the distinction is not clear, clinicians should treat patients as though they have orbital cellulitis. Both conditions are more common in children than in adults, and preseptal cellulitis is much more common than orbital cellulitis. (Source:UpToDate)

Summary

- Pharmacodainamics: It is the biological and therapeutic effect of the drug (mechanism of action).

- Pharmacokinetics: It is the absorption, distribution, metabolism, and excretion of the drug.

-Factors influencing local drug penetration into ocular tissue: Drug concentration and solubility, Viscosity, Lipid solubility, Surfactants, PH, Drug tonicity.

-Types: Eye drops, ointments, peri-ocular injection, intraocular injection, sustained release device, systemic drugs.

-Ocular pharmacotheraputics include: Cholinergic agonists, cholinergic antagonists, adrenergic agonists, adrenergic antagonists, carbonic anhydrase inhibitor, osmotic agents , prostaglandin analogs, anti-microbial, anti-inflammatory, ocular diagnostic drugs, local anesthetics, other ocular preparations, intraviteal injection.

(Which was explained in details in the previous pages)

Class	Color of Bottle Cap	
Anti-infectives	Tan	
Anti-inflammatories/steroids	Pink	
Mydriatics and cycloplegics	Red	
Nonsteroidal anti-inflammatories	Gray	
Miotics	Dark Green	
Beta-blockers	Yellow	
Beta-blocker combinations	Dark Blue	
Adrenergic agonists	Purple	
Carbonic anhydrase inhibitors	Orange	
Prostaglandin analogues	Turquoise	

Some of the doctors were asking about these colors in the clinics so go through it quickly

MCQs:

1. All of the following medications cause cycloplegia except:

A. Atropine B. Cyclopentolate

C. Homatropine D. Scopolamine. E. Phenylephrine

2. Which of the following is a miotic drug:

A.Tetracycline B.Physostigmine

C. Scopolamine D. Pilocarpine

3. Which of the following medications is contraindicated in a patient with sulfa allergy:

A. Acetazolamide B. Physostigmine

C. Pilocarpine D. Phenylephrine

4. Your patient is a student who has a final exam today, he came to your clinic to do a fundus exam which medication should you use in this case?

A. Tropicamide C. Atropine

B. Phenylephrine D. Physostigmine

Answers:

1. E
2. D
3. A
4. B "because he needs to accommodate during the exam and this drug causes mydriasis only without cycloplegia"

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