#5 - Ocular Pharmacology and Toxicology

Done by: Shahd Alawwad.

Revised by: Alanoud Alyousef

Team Leader: *Shaikha Aldossari*

Doctor's note Team's note Not important Important 431 teamwork in a yellow box

Objectives:

Not given

1) Ocular pharmacology

- Cholenergic agonist
- Cholenergic antagonist
- Adrenergics Agonist
- Adrenergics Antagonist
- Prostaglandin agonist
- Local anesthetics
- Carbonic anhydrase
- Ocular diagnostic dugs
- Osmotic agent
- Anti-inflammatory (Steroids, NSAID, Anti-allergics)
- Anti-Microbial (Ani-biotics, Anti-viral , Anti-fungal)

2) Ocular Toxicology

General pharmacological principles

Pharmacodynamics:

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

Pharmacokinetics:

* It is the absorption, distribution, metabolism, and excretion of the drug.
* A drug can be delivered to ocular tissue as:
  - Locally: (Eye drop, Ointment, Periocular injection, Intraocular injection)
  - Systemically: (Orally, IV.)

Factors influencing local drug penetration into ocular tissue: (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.)
* **Viscosity:** addition of methylcellulose and polyvinyl alcohol increases drug penetration by increasing the contact time with the cornea and altering corneal epithelium
* **Lipid solubility:** because of the lipid rich environment of the epithelial cell membranes, the higher lipid solubility the more the penetration.
* **Surfactants:** the preservatives used in ocular preparations alter cell membrane in the cornea and increase drug permeability e.g. benzylkonium and thiomersal
* **PH:** the normal tear pH is 7.4 and if the drug pH is much different, this will cause reflex tearing.

*** Drug tonicity:** when an alkaloid drug is put in relatively alkaloid medium, the proportion of the uncharged form will increase, thus more penetration.

Eye drops:

* Eye drops- most common
* one drop = 50 µl
* Volume of conjunctival cul-de-sac 7-10 µl
* Measures to increase drop absorption:
  -Wait 5-10 minutes between drops.
  -compress lacrimal sac. (To avoid drops escape through NasoLacrimal Duct)
  -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 chamber) or intravitreal
* E.g. – Intracameral acetylcholine (miochol) :
During cataract surgery – Intravitreal antibiotics in cases of endophthalmitis – Intravitreal steroid in macular edema – Intravitreal Anti-VEGF for DR. (Diabetic Retinopathy)

Sustained-release devices:

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

Systemic drugs:

* Oral or IV
* Factor influencing systemic drug penetration into ocular tissue:
– lipid solubility of the drug: more penetration with high lipid solubility.
– Protein binding: more effect with low protein binding
– Eye inflammation: more penetration with ocular inflammation.

Ocular pharmacotherapeutics

Cholinergic agonists:

Directly acting agonists:	Indirectly acting (anticholinesterases): *More potent with longer duration of action*	
E.g. pilocarpine, acetylcholine (miochol), carbachol (miostat)	**Reversible inhibitors**	Irreversible
Uses: miosis, glaucoma	e.g. physostigmine	e.g. phospholine iodide
Mechanisms: * Miosis by contraction of the iris sphincter muscle. * increases aqueous outflow through the trabecular meshwork by longitudinal ciliary muscle contraction. * Accommodation by circular ciliary muscle contraction.	**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), headache, cataract, miotic cysts, and rarely retinal detachment. (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!) ***Contra indicated :** -in angle closure glaucoma, asthma, Parkinsonism -causes apnea if used with succinylcholine or procaine

Cholinergic Antagonists:

E.g. tropicamide, cyclopentolate, homatropine, scopolamine, atropine
* Cause mydriasis (by paralyzing the sphincter muscle) with cycloplegia (by paralyzing the ciliary muscle, so there is loss of accommodation)

* **Uses:** fundoscopy, cycloplegic refraction, 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 delerium
– **Treatment** by discontinuation or physostigmine.

Adrenergic Agonists:

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, prophylaxis against IOP spiking after glaucoma laser procedures
Side effects: headache, arrhythmia, increased blood pressure, conjunctival adrenochrome (it's reminant of the depevefrin) , cystoid macular edema in aphakic (No lens) eyes (in trauma or surgical cataract removal, so the accommodation lost and expected hypermetropia. **–Contraindicated:** in closed angle glaucoma	**Side effects**: Can cause significant increase in blood pressure specially in infant and susceptible adults – Rebound congestion . – precipitation of acute angle-closure glaucoma in patients with narrow angles	**Side effects:** **<u>local</u>:** allergic reaction, mydriasis, lid retraction, conjunctival blanching **<u>systemic</u>:** oral dryness, headache, fatigue, drowsiness, orthostatic hypotension, vasovagal attacks **Contraindications:** infants, MAO inhibitors users

Adrenergic Antagonists:

Alpha adrenergic antagonists	Beta-adrenergic blockers ***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 phenylepherine Not widely used	**Uses:** glaucoma
	Side effects: bronchospasm (less with betaxolol), cardiac impairment

Carbonic Anhydrase Inhibitors

* E.g. acetazolamide, methazolamide, dichlorphenamide, dorzolamide, brinzolamide.
* **Uses**: glaucoma, cystoid macular edema, pseudotumour cerebri
* **Mechanism**: aqueous suppression
* **Side effects**:
myopia, paresthesia (in extremities) , anorexia, GI upset, headache, altered taste and smell, Na and K depletion, metabolic acidosis, renal stone, bone marrow suppression "aplastic anemia"
* **Contraindication:**
sulpha allergy, digitalis users, pregnancy.

Osmotic Agents

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

Prostaglandin Analogues

* E.g. latanoprost, bimatoprost, travoprost, unoprostone
* **Uses**: glaucoma
* **Mechanism**: increase uveoscleral aqueous outflow
* **Side effects**:
darkening of the iris (heterochromia iridis), lengthening and thickening of eyelashes, intraocular inflammation, macular edema

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

<table>
<tr><th colspan="2">Corticosteroids
– Mechanism: inhibition of arachidonic acid release from phospholipids by inhibiting phosphlipase A2</th><th>NSAID
Mechanism: inactivation of cyclooxygenase</th><th>Anti-allergics</th></tr>
<tr><td>Topical
– E.g. fluorometholone, remixolone (weakest) , prednisolone, hydrocortisone (both are the strongest), dexamethasone.</td><td>Systemic:
– E.g. prednisolone, cortisone</td><td>E.g. ketorolac, diclofenac, flurbiprofen</td><td rowspan="2">* Avoidance of allergens, cold compress, lubrications.

*Antihistamines (pheniramine, levocabastine)

*Decongestants (naphazoline, phenylepherine, tetrahydrozaline- not preferable as it causes rebound congestion)

*Mast cell stabilizers (. cromolyn, lodoxamide, pemirolast, nedocromil, olopatadine = the best.)</td></tr>
<tr><td colspan="2">Uses:
postoperatively, anterior uveitis, severe 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.</td><td>Uses:
posterior uveitis, optic neuritis, temporal arteritis with anterior ischemic optic neuropathy</td><td>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)</td></tr>
</table>

Side effects: susceptibility to infections (especially fungal) , glaucoma, cataract, ptosis, mydriasis, scleral melting, skin atrophy	**Side effects:** Local: posterior subcapsular cataract, glaucoma, central serous retinopathy Systemic: suppression of pituitary-adrenal axis, hyperglycemia, osteoporosis, peptic ulcer, psychosis	**Side effects:** stinging	* NSAID (ketorolac) *Steroids (fluorometholone, remixolone, prednisolone) * 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
*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	*Trifluridine more corneal penetration can treat herpetic iritis * Ganciclovir used intravenously for CMV retinitis

*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.	permeability – e.g. miconazole, *ketoconazole Flucytocine – act by inhibiting DNA synthesis. 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		

Ocular Diagnostic Drugs:

Fluorescein dye **– Available as drops or strips**	Rose bengal stain. **Stains devitalized epithelium**
– Uses: stain corneal abrasions, applanation tonometry, detecting wound leak, NLD obstruction, fluorescein angiography.	**– Uses:** **severe dry eye, herpetic keratitis**
– Caution: *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, allergic reaction rarely.	

Other Ocular Preparations:

Lubricants:
– drops or ointments
– Polyvinyl alcohol, cellulose, methylcellulose – Preserved or preservative free.

Intraviteal injection:

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

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

***Uses**:

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

Ocular Toxicity:

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
* Causes acute angle-closure glaucoma (acute eye pain, redness, blurred vision, haloes).(moves iris lense diaphragm 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)

Clinical features of preseptal and orbital cellulitis

Clinical feature	Preseptal cellulitis	Orbital cellulitis
Eyelid swelling with or without erythema	Yes	Yes
Eye pain/tenderness	May be present	Yes; may cause deep eye pain
Pain with eye movements	No	Yes
Proptosis	No	Usually, but may be subtle
Ophthalmoplegia +/- diplopia	No	Yes
Vision impairment	No	May be present*
Chemosis	Rarely present	May be present
Fever	May be present	Usually present
Leukocytosis	May be present	May be present

* An afferent pupillary defect may signal impending visual loss.

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)

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"

If you have any questions/suggestions regarding Ophthalmology teamwork please via:

432OphthalmologyTeam@gmail.com