

Ocular Pharmacology and Toxicology

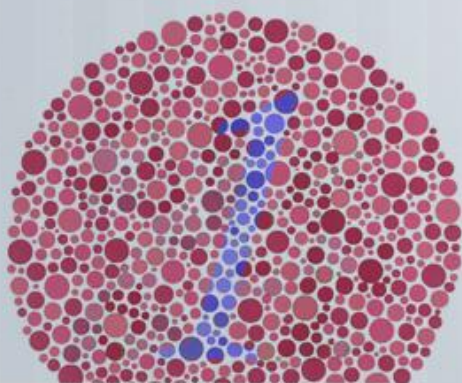
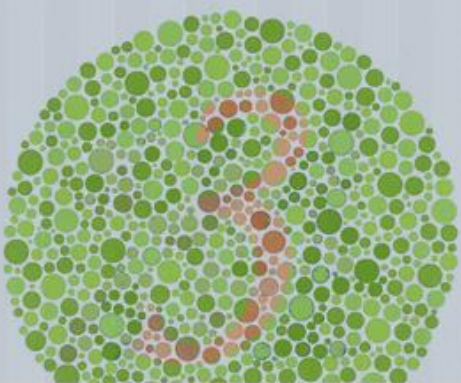
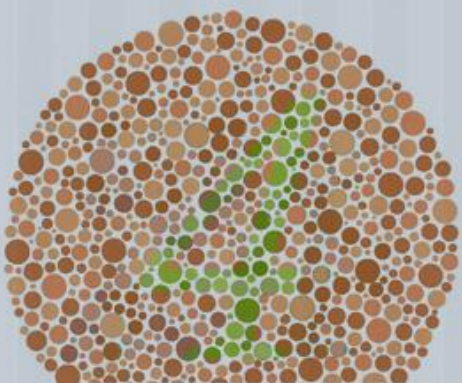


431
Teams
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Ophthalmology Team

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From slides Doctor's Notes Team's Notes From the book Important

Ocular Pharmacology and 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

- The study of the mechanisms of absorption, distribution of an administered drug, metabolism (the chemical changes of the substance in the body) & the effects and routes of excretion of the drug.
- To achieve a therapeutic effect, a drug must reach its site of action in sufficient concentration.
- Locally:
 - Eye drop.
 - Ointment.
 - Periocular injection.
 - Intraocular injection.
- 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% but limited by <u>reflex tearing</u> (for pilocarpine if concentration > 4%: ↓ penetration).
Viscosity	Addition of methylcellulose and polyvinyl alcohol increases drug penetration by <u>increasing the contact time</u> with the cornea and <u>altering corneal epithelium</u> .
Lipid Solubility	Because of the lipid rich environment of the epithelial cell membranes, <u>the higher lipid solubility the more the penetration</u> .
Surfactants	The <u>preservatives</u> used in ocular preparations <u>alter cell membrane</u> in the cornea and <u>increase drug permeability</u> 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.
Tonicity	When an alkaloid drug is put in relatively alkaloid medium, the proportion of the uncharged form will increase, thus more penetration. (So pH: 7.5 is better than 7.3).

LOCAL DRUGS

Eye drops	<ul style="list-style-type: none"> • <u>Most Common.</u> • One drop: 50 µl. • Volume of conjunctival cul-de-sac 7-10 µl. • Measures to increase drop absorption: <ul style="list-style-type: none"> ○ Wait 5-10 minutes between drops. (If 2 different drugs). ○ Compress lacrimal sac. ○ Keep lids closed for 5 minutes after instillation.
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Ointment	<ul style="list-style-type: none"> • Increase the contact time of ocular medication to ocular surface thus better effect. • It has the disadvantage of <u>vision blurring</u>. (Usually prescribed at night time). • The drug has to be high lipid soluble with some water solubility to have the maximum effect as ointment.
Peri-Ocular Injection	<ul style="list-style-type: none"> • They reach behind iris-lens diaphragm better than topical application <ul style="list-style-type: none"> ○ E.g. subconjunctival, subtenon, peribulbar, or retrobulbar • This route bypass the conjunctival and corneal epithelium which is <u>good for drugs with low lipid solubility</u> (e.g. penicillins). • Also steroid and local anesthetics can be applied this way.
Intraocular injection	<p>Intracameral or intravitreal. E.g.</p> <ul style="list-style-type: none"> • Intracameral acetylcholine (miochol) during cataract surgery. • Intravitreal antibiotics in cases of endophthalmitis. • Intravitreal steroid in macular edema. • Intravitreal Anti-VEGF for DR.

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 sustained-release intraocular device, Collagen shields.

SYSTEMIC DRUGS

Factor influencing systemic drug penetration into ocular tissues:

- **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. (Degradation of blood-ocular barrier, so in case of eye inflammation it is necessary to decrease the medication dose).

Before we go to the list of medications, let us take a look at the receptors of the intraocular muscles

Target	Sympathetic (Adrenergic)	Parasympathetic (Muscarinic)
Pupil Dilator Muscle	α 1: Dilation (causes mydriasis)	-
Iris Sphincter Muscle	-	M3: Contract (causes miosis)
Ciliary Muscle	β 2: Relaxes (causes long-range focus)	M3: Contracts (causes short-range focus)

So when you use a medication which works by stimulating α 1 receptors only, it will cause dilation to the pupil dilator muscle and therefore mydriasis without cycloplegia because it does not paralyze the ciliary muscle! To induce cycloplegia (important in refraction during eye examination) we have to use a Muscarinic (cholinergic) receptor antagonist (blocker) like tropicamide to stop the contraction of ciliary muscle and therefore paralyze it (effect= mydriasis with cycloplegia).

Ocular Pharmacotherapeutics

Cholinergic Agonists				
	Examples	Uses	Mechanism	Side Effects
Directly Acting	Pilocarpine	Miosis Glaucoma	Miosis by contraction of the iris sphincter muscle.	Local: diminished vision (myopia), headache, cataract, miotic cysts, and rarely retinal detachment.
	Acetylcholine (miochol)		Increases aqueous outflow through the trabecular meshwork by longitudinal ciliary muscle contraction.	
	Carbachol (miostat)		Accommodation by circular ciliary muscle contraction	Systemic: lacrimation, salivation, perspiration, bronchial spasm, urinary urgency, nausea, vomiting, and diarrhea.
Indirectly Acting	Reversible: "Stigmines" Physostigmine	Glaucoma Lice Infestation of Lashes	Inhibition of Acetylcholinesterase	Cause CNS Side effects that's why not widely used in glaucoma.
	Irreversible: Phospholine iodide	Accommodative esotropia	Irreversible inhibition of Acetylcholinesterase They induce the accommodation (+miosis) passively without having impulses from the brain so this eliminates convergence of the eyes.	Iris cyst (as any cholinergic) and anterior subcapsular cataract (iris will be rubbing the anterior part of the lens). Contraindicated in angle closure glaucoma, asthma, Parkinsonism Causes apnea if used with succinylcholine or procaine

Cholinergic Antagonists (Anti-Cholinergics/Anti-Muscarinic)				
Examples	Uses	Mechanism	Side Effects	
Anti-Cholinergics usually have a red top bottle. Tropicamide Cyclopentolate Homatropine Scopolamine atropine	Fundoscopy	mydriasis (by paralyzing the sphincter muscle) with cycloplegia (by paralyzing the ciliary muscle)	Local: allergic reaction, blurred vision.	
	Cycloplegic refraction Anterior uveitis (to prevent posterior Synechia)		Systemic: nausea, vomiting, pallor, vasomotor collapse, constipation, urinary retention, and confusion especially in children they might cause flushing, fever, tachycardia, or delirium. Treatment by DC or Physostigmine.	

Adrenergic Agonists			
Type	Example	Uses	Side Effects and Contraindications
Non Selective Agonist (α_1 , α_2 , β_1 , β_2)	epinephrine depevefrin (pro-drug of epinephrine)	Glaucoma (Open angle)	headache, arrhythmia, increased blood pressure, conjunctival adrenochrome (Pigmented deposits for chronic users), cystoid macular edema in aphakic (who have their lens removed don't confuse with pseudophakic) eyes C/I in closed angle glaucoma
α_1 Agonist	phenylephrine	mydriasis (without cycloplegia , so patient can still see near objects), decongestant	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
α_2 Agonist	Brimonidine Apraclonidine "Most common adrenergics used for treating glaucoma"	Glaucoma treatment, prophylaxis against IOP spiking after glaucoma laser procedures (They decrease aqueous production, and increase uveoscleral outflow "not through the angle") "2 Mechanisms!"	Local: allergic reaction, mydriasis, lid retraction, conjunctival blanching. "Causes Muller's muscle contraction thus lid retraction, if the patient used it in one eye he will have un-equal palpebral fissures " Systemic: oral dryness, headache, fatigue, drowsiness, orthostatic hypotension, vasovagal attacks Contraindications: infants, MAO inhibitors users

Adrenergic Antagonists			
Type	Example	Uses	Side Effects
Alpha antagonists	thymoxamine dapiprazole	"Not widely used" to reverse pupil dilation produced by phenylephrine	
Beta blockers	non-selective timolol, levobunolol, metipranolol, carteolol selective betaxolol (beta 1 "cardioselective")	Glaucoma "reduce aqueous formation"	bronchospasm (less with betaxolol), cardiac impairment

Miscellaneous				
Class	Example	Uses	Mechanism	Side Effects
Carbonic Anhydrase inhibitors	Acetazolamide Methazolamide dichlorphenamide dorzolamide brinzolamide	Glaucoma cystoid macular edema pseudotumour cerebri	Aqueous suppression Contraindication: sulpha allergy, digitalis users, pregnancy	myopia, paresthesia "Peripheral numbness, a universal side effect, if not present → patient is not compliant", anorexia, GI upset, headache, altered taste and smell, Na and K depletion , metabolic acidosis, renal stone, bone marrow suppression "aplastic anemia".
Osmotic Agents	glycerol 50 syrup	Reduce IOP Significantly	Dehydrate Vitreous Body	Nausea and Hyperglycemia (Don't use with diabetics)
	Mannitol 20% IV			fluid overload and not used in heart failure
Prostaglandin Analogues	latanoprost, bimatoprost, travoprost, unoprostone	Glaucoma	increase uveoscleral aqueous outflow (Remember: This is not the main outflow!)	darkening of the iris (heterochromia iridis), lengthening and thickening of eyelashes, intraocular inflammation, macular edema

Anti-Inflammatory					
Type	Examples	Uses	Mechanism	Side Effects	
Corticosteroids	Topical	fluorometholone, rimexolone, prednisolone, dexamethasone, hydrocortisone	postoperatively, anterior uveitis, severe allergic conjunctivitis, vernal keratoconjunctivitis, prevention and suppression of corneal graft rejection, episcleritis, scleritis	inhibition of arachidonic acid release from phospholipids by inhibiting phospholipase A2	susceptibility to infections, glaucoma, cataract , ptosis, mydriasis, scleral melting, skin atrophy
	Systemic	prednisolone, cortisone	posterior uveitis, optic neuritis, temporal arteritis with anterior ischemic optic neuropathy		Local: posterior subcapsular cataract , glaucoma, central serous retinopathy Systemic: suppression of pituitary-adrenal axis, hyperglycemia, osteoporosis, peptic ulcer, psychosis
NSAIDs	ketorolac, diclofenac, flurbiprofen	postoperatively, mild allergic conjunctivitis, episcleritis, mild uveitis, cystoid macular edema, preoperatively to prevent miosis during surgery "to inhibit prostaglandin which is known to constrict the pupil"	inactivation of cyclooxygenase enzyme	Stinging	

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

ANTIBIOTICS

- Penicillins
 - Cephalosporins
 - Sulfonamides
 - Tetracyclines
 - Chloramphenicol
 - Aminoglycosides
 - Fluoroquinolones
 - Vancomycin
 - Macrolides
- Used **topically** in prophylaxis (pre and postoperatively) and treatment of ocular bacterial infections.
 - Used **orally** for the treatment of preseptal cellulitis e.g. amoxicillin with clavulonate, cefaclor.
 - Used **intravenously** for the treatment of orbital cellulitis e.g. gentamicin, cephalosporin, vancomycin, flagyl.
 - Can be injected **intravitally** for the treatment of endophthalmitis.
 - **Trachoma** 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 “hourly”.
 - **Bacterial conjunctivitis** is usually self-limited but topical erythromycin, aminoglycosides, fluoroquinolones, or chloramphenicol can be used.

ANTI-FUNGAL

Uses: fungal keratitis, fungal endophthalmitis.

- Polyenes
 - Damage cell membrane of susceptible fungi.
 - E.g. amphotericin B, natamycin.
 - Side effect: nephrotoxicity.
- Imidazoles
 - Increase fungal cell membrane permeability. E.g. miconazole, ketoconazole.
- Flucytocine
 - Act by inhibiting DNA synthesis.

ANTI-VIRALS

- Acyclovir
 - Interact with viral thymidine.
 - Kinase (selective).
 - Used in herpetic keratitis.
- Trifluridine
 - More corneal penetration.
 - Can treat herpetic iritis.
- Ganciclovir
 - Used intravenously for CMV.
 - Retinitis.

OCULAR DIAGNOSTIC DRUGS

Fluorescein dye

- Available as drops or strips
 - Uses: stain corneal abrasions, applanation tonometry, detecting wound leak, NLD obstruction, fluorescein angiography
- **Caution!**
 - Stains soft contact lens.
 - Fluorescein drops can be contaminated by *Pseudomonas* sp.

Rose Bengal Stain

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

LOCAL ANESTHETICS

Topical

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

Orbital infiltration

- Peribulbar or retrobulbar.
- Cause anesthesia and akinesia for intraocular surgery.
- E.g. lidocaine, bupivacaine.

LUBRICANTS

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

Ocular Toxicology

COMPLICATIONS OF TOPICAL ADMINISTRATION

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

Drug	Effect
Amiodarone	A cardiac arrhythmia drug. Causes optic neuropathy (mild decreased vision, visual field defects, bilateral optic disc swelling). Also causes corneal vortex keratopathy (corneal verticillata) which is whorl-shaped pigmented deposits in the corneal epithelium.
Digitalis	A cardiac failure drug. Causes chromatopsia (objects appear yellow) with overdose.
Chloroquines	E.g. chloroquine, hydroxychloroquine Used in malaria, rheumatoid arthritis, SLE Cause vortex keratopathy (corneal verticillata) which is usually asymptomatic but can present with glare and photophobia & retinopathy (bull's eye maculopathy)
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 <u>high dosage</u>
Diphenylhydantoin	An epilepsy drug Causes dosage-related cerebellar-vestibular effects: Horizontal nystagmus in lateral gaze Diplopia, ophthalmoplegia Vertigo, ataxia Reversible with the discontinuation of the drug
Topiramate	A drug for epilepsy Causes acute angle-closure glaucoma (acute eye pain, redness, blurred vision, haloes). Treatment of this type of acute angle-closure glaucoma is by cycloplegia and topical steroids (rather than iridectomy) with the discontinuation of the drug
Ethambutol	An anti-TB drug Causes a dose-related optic neuropathy Usually reversible but occasionally permanent visual damage might occur

AGENTS THAT CAN CAUSE TOXIC OPTIC NEUROPATHY

- **Methanol (IMP!!!)**
- Ethylene glycol (antifreeze)
- **Chloramphenicol**
- **Isoniazid**
- high-protein diet
- Carbon monoxide
- **Lead**
- **Mercury**
- Quinine
- Pernicious anemia (vitamin B-12 malabsorption phenomenon)
- Vincristine and methotrexate (chemotherapy medicines)
- Sulfonamides
- Melatonin with Zoloft (sertraline Pfizer)
- Radiation unshielded exposure to >3,000 rads).
- **Ethambutol**
- **Digitalis**
- Chloroquine
- Thallium (alopecia, skin rash, severe vision loss)
- Malnutrition with vitamin B-1 deficiency
- **Streptomycin**
- **Amiodarone**
- methotrexate

HMG-COA REDUCTASE INHIBITORS (STATINS):

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

OTHER AGENTS

Methanol	Optic atrophy and blindness (Patient presents with history of alcohol drinking).
Contraceptive pills	Pseudotumour 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.

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
- B. Phenylephrine
- C. Atropine
- D. Physostigmine

5. Which of the following medications has to be avoided in a patient with heart failure:

- A. Acetazolamide
- B. Tetracycline
- C. Mannitol
- D. Non Selective β Blocker

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"
5. C