

Ocular pharmacology and 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

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.

A drug can be delivered to ocular tissue as:

Locally	systemically
Eye drop Ointment Periocular injection Intraocular injection	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 <u>limited by reflex tearing</u>
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 preservatives used in ocular preparations <u>alter cell membrane in the cornea</u> 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

Local Drugs :

Eye drops	<p>Eye drops- most common</p> <p>One drop = 50 µl</p> <p>Volume of conjunctival cul-de-sac 7-10 µl</p> <p>Measures to increase drop absorption:</p> <ul style="list-style-type: none"> -wait 5-10 minutes between drops -compress lacrimal sac -keep lids closed for 5 minutes after instillation
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Ointments	Increase the contact time of ocular medication to ocular surface thus better effect . It has the disadvantage of <u>vision blurring</u> . 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 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

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 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

	Example	Uses	Mechanism	Side effects
Cholinergic Agonists				
Directly acting agonists	pilocarpine, acetylcholine (miochol), carbachol (miostat)	miosis, glaucoma	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	Local: diminished vision (<u>myopia</u>), <u>headache</u> , cataract, miotic cysts, and rarely retinal detachment Systemic: lacrimation, salivation, perspiration, bronchial spasm, urinary urgency, nausea, vomiting, and diarrhea

Indirectly acting (anticholinesterases)	More potent with longer duration of action		
-Reversible inhibitors	physostigmine	glaucoma and lice infestation of lashes	can cause CNS side effects
-Irreversible	phospholine iodide	In accommodative esotropia	iris cyst and anterior subcapsular cataract C/I in angle closure glaucoma, asthma, Parkinsonism causes apnea if used with succinylcholine or procaine
Cholinergic Antagonists			
tropicamide, cyclopentolate, homatropine, scopolamine, atropine .	fundoscopy, cycloplegic refraction, anterior uveitis	mydriasis (by paralyzing the sphincter muscle) with cycloplegia (by paralyzing the ciliary muscle)	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 DC or physostigmine
Adrenergic Agonists			
Non-selective agonists (α_1, α_2, β_1, β_2)	epinephrine, depevefrin (pro-drug of epinephrine)	glaucoma	headache, arrhythmia, increased blood pressure, conjunctival adrenochrome, cystoid macular edema in aphakic eyes C/I in closed angle glaucoma
Alpha-1 agonists	phenylephrine	mydriasis (<u>without</u> cycloplegia), decongestant	Can cause significant <u>increase in blood pressure</u> specially in infant and susceptible adults Rebound congestion precipitation of acute angle-closure glaucoma in patients with narrow angles
Alpha-2 agonists <u>Contraindications:</u> infants, MAO inhibitors users	brimonidine, apraclonidine	glaucoma treatment, prophylaxis against IOP spiking after glaucoma laser procedures	decrease aqueous production, and increase uveoscleral outflow local: allergic reaction, mydriasis, lid retraction, conjunctival blanching systemic: oral dryness, headache, fatigue, drowsiness, orthostatic hypotension, vasovagal attacks

Alpha adrenergic antagonists	thymoxamine, dapiprazole	to reverse pupil dilation produced by phenylephrine		NOT WIDELY USED
Beta-adrenergic blockers	non-selective: timolol, levobunolol, metipranolol, carteolol selective: betaxolol (beta 1 “cardioselective”)	glaucoma	reduce the formation of aqueous humor by the ciliary body	<u>bronchospasm</u> (less with betaxolol), cardiac impairment
Carbonic anhydrase inhibitors <u>Contraindication:</u> sulpha allergy, digitalis users, pregnancy	acetazolamide, methazolamide, dichlorphenamide, dorzolamide, brinzolamide.	glaucoma, cystoid macular edema, pseudotumour cerebri	aqueous suppression	myopia, parasthesia, anorexia, GI upset, headache, altered taste and smell, Na and K depletion, metabolic acidosis, renal stone, bone marrow suppression “aplastic anemia”
Prostaglandin analogues	latanoprost, bimatoprost, travoprost, unoprostone	glaucoma	increase uveoscleral aqueous outflow	darkening of the iris (<u>heterochromia iridis</u>), lengthening and thickening of eyelashes, intraocular inflammation, macular edema
Osmotic agents	<ul style="list-style-type: none"> glycerol 50% syrup Mannitol 20% IV 	Dehydrate vitreous body which reduce IOP significantly		<ul style="list-style-type: none"> nausea, hyperglycemia fluid overload and not used in heart failure

Anti-inflammatory

	Examples	Uses	Mechanism	Side effects
Corticosteroids				
Topical	fluorometholone, remixelone, 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	<u>susceptibility to infections</u> , <u>glaucoma</u> , <u>cataract</u> , ptosis, mydriasis, scleral melting, skin atrophy
Systemic	prednisolone, cortisone	posterior uveitis, optic neuritis, temporal arteritis with anterior ischemic optic neuropathy	Local: <u>posterior subcapsular cataract</u> , glaucoma, central serous retinopathy Systemic: suppression of pituitary-adrenal axis, hyperglycemia, osteoporosis, peptic ulcer, psychosis	
NSAID				
ketorolac, diclofenac, flurbiprofen	postoperatively, mild allergic conjunctivitis, episcleritis, mild uveitis, cystoid macular edema, preoperatively to prevent miosis during surgery		inactivation of cyclo-oxygenase	stinging
Anti-allergics				
Avoidance of allergens, cold compress, lubrications				
Antihistamines	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	
Steroids	fluorometholone, remixelone, prednisolone		Posterior subcapsular cataracts Glaucoma Papilledema Predisposition to fungal infections	

Antifungals				
Polyenes	amphotericin B, natamycin	fungal keratitis, fungal endophthalmitis	damage cell membrane of susceptible fungi	nephrotoxicity
Imidazoles	miconazole, ketoconazole		increase fungal cell membrane permeability	
Flucytocine			act by inhibiting DNA synthesis	
Antiviral				
Acyclovir	herpetic keratitis		interact with viral thymidine kinase(selective)	
Trifluridine	herpetic iritis		more corneal penetration	
Ganciclovir	intravenously for CMV retinitis			
Antibiotics				
Penicillins	<ul style="list-style-type: none">-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-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.-Bacterial conjunctivitis is usually <u>self limited</u> but topical erythromycin, aminoglycosides, fluoroquinolones, or chloramphenicol can be used			
Cephalosporins				
Sulfonamides				
Tetracyclines				
Chloramphenicol				
Aminoglycosides				
Fluoroquinolones				
Vancomycin				
macrolides				

Ocular diagnostic drugs

	Uses	Caution
Fluorescein dye Available as drops or strips	stain corneal abrasions, applanation tonometry, detecting wound leak, NLD obstruction, fluorescein angiography	stains soft contact lens can be contaminated by Pseudomonas sp
Rose bengal stain	Stains devitalized epithelium severe dry eye, herpetic keratitis	

Local anesthetics

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

Orbital infiltration peribulbar or retrobulbar	.lidocaine, bupivacaine	cause anesthesia and akinesia for intraocular surgery
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Other ocular preparations

Lubricants	Polyvinyl alcohol, cellulose, methylcellulose	drops or ointments Preserved or preservative free
Intravitreal Injections	AntiVEGF (antivascular endothelial growth factors): bevacizumab (Avastin) Ranibizumab (Lucentis).	Age related macular degeneration DM (macular edema,PDR). Central retinal vein occlusion, BRVO

Ocular toxicology

Complications of topical administration	
Mechanical injury from the bottle	corneal abrasion
Pigmentation	Epinephrine adrenochrome
Ocular damage	topical anesthetics, benzylkonium
Hypersensitivity	atropine, neomycin, gentamicin
Systemic effect	topical phenylephrine increase BP

Drugs	Effect
Amiodarone	A cardiac arrhythmia drug Causes optic neuropathy (mild decreased vision, visual field defects, bilateral optic disc swelling)&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)
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
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 , Ethylene glycol (antifreeze) , Chloramphenicol , Isoniazid , Ethambutol
 Digitalis , Chloroquine , Streptomycin , Amiodarone , Quinine
 Vincristine and methotrexate (chemotherapy medicines) , Sulfonamides
 Melatonin with Zoloft (sertraline, Pfizer)
 high-protein diet , Carbon monoxide , Lead , Mercury
 Thallium (alopecia, skin rash, severe vision loss) , Malnutrition with vitamin B-1 deficiency
 Pernicious anemia (vitamin B-12 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

Drugs	Effect
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.

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