



Lecture 2

Pharmacology of drugs acting on the eye

- Additional Notes
- Important
- Explanation –Extra-

Drugs can be delivered to ocular tissue as:						
Locall	y (Topically): More common	Systemically				
Eye drops	 Eye drops- most common one drop = 50 µl Their contract time with the tissue is low → should be used several times (every 4 hours mostly) 	Orally	IV			
Ointments مراهم	Increase the contact time of ocular medication to ocular surface thus better effect Disadvantage: The drug has to be high lipid soluble to have the maximum effect as ointment	Factor influencing system into ocular tissue: 1. lipid solubility of the penetration with hi 2. Protein binding: ma	e drug: more gh lipid solubility.			
Peri-ocular injection	 Sub-conjunctival, retro-bulbar (behind the eyeball) or peri-bulbar (around eye ball). Reach behind iris-lens diaphragm better than topical application Bypass the conjunctival and corneal epithelium which is good for drugs with low lipid solubility (e.g. penicillin's) Steroid and local anesthetics can be applied this way 	protein binding. 3. Eye inflammation: rewith ocular inflamn Superior oblique muscle Levator palpebrae superioris muscle Superior rectus muscle	·			
Intraocular injection	 Intra-cameral (inside chamber) or intra-vitreal (intra-vitreous): Intra-cameral acetylcholine or lidocaine during cataract surgery Intra-vitreal antibiotics in cases of endophthalmitis (inflammation of internal coats of eye) Intra-vitreal steroid in macular edema 	Medial rectus muscle Lateral rectus muscle (cut)	Optic nerve (II) Lateral rectus muscle (cut) Inferior oblique muscle			
Sustained release preparations		Inferior rectus muscle	1. Subconjunctival route 2. Retrobulbar route 3. Peribulbar route			

Receptor	Organ	Action
	Eye	Dilates pupils by Contraction of dilator Pupillae (Active mydriasis).
	Blood vessels	Constriction of BV in skin & peripherals (except the heart and skeletal muscle).
a	Gl	Sphincter: Constriction (retention).
$oldsymbol{lpha_1}$ (constriction)	GU	Urinary sphincter: Constriction.Uterus, pregnant: Contraction.PENIS: Ejaculation.
	Secretory glands	Sweat : Localized secretion.
	Secretory glands	 Intestinal : Inhibition. Salivary glands: ✓ Salivation.
α_2	Metabolism	 Pancreas (b cells): insulin release. Adrenergic terminals: inhibits NE release.
0	Heart	 - ♠ heart rate (chronotropic). - ♠ Force of contraction (Inotropic). - ♠ Conduction velocity and automaticity (Dromotropic).
β_1	Blood vessels	- ★ systolic
	Kidney	- ↑ renin release.
	Eye	Ciliary muscle : Relaxation. (accommodation for far vision)
		Bronchial muscle : Relaxation (Bronchodilatation).
β2	Blood vessels	 Relaxation of BV (Vasodilatation) → Coronary & skeletal. Abundant on blood vessels serving the heart, liver and skeletal muscle.
(Relaxation)		→ motility and tone.
		Bladder wall : Relaxation.Uterus, pregnant : relaxation (Tocolysis).
	Metabolism	Skeletal muscle : Glycogenolysis , ◆contractility .Liver : ◆Glucose.
β_3	Fat cells	Lipolysis.

RECALL

Autonomic Nerve supply of the Eye

Parasympathetic N.S. Sympathetic N.S. Contraction of dilator Pupillae (Active Constriction of the pupillary sphincter mydriasis) α 1 muscle (miosis) - Mydriasis mean the iris go to the back. Contraction of the ciliary muscle Relaxation of ciliary muscles (accommodation for near vision). (accommodation for far vision) β 2 Decrease in intraocular pressure \(\brace \) IOP. Increase in intraocular pressure Increases aqueous outflow through the Lacrimation α 1 trabecular meshwork into canal of **Vasoconstriction** of conjunctival blood Schlemm by ciliary muscle contraction. vessels $\alpha 1$ $\alpha \& \beta$ receptors in the blood vessels of Increased lacrimation the ciliary processes → help in regulation Conjunctival Vasodilatation of aqueous humour formation.

Eye	Parasympathetic N.S.	Sympathetic N.S.
Iris: 1- radial muscle. 2- circular muscle.	 No effect Contraction (miosis) M3 	 Contraction (Mydriasis) α1 No effect
Ciliary muscle	Contraction M3	Relaxation \$2
Accommodation	for near vision	for far vision
Conjunctival blood vessels	Conjunctival Vasodilatation	Conjunctival Vasoconstriction

Accommodation Mydriasis Distant object Near object

Circular muscle it receives parasympathetic action (<u>miosis</u>) radial muscle receive sympathatic action (<u>mydriasis</u>).

Drugs acting on parasympathetic system

Choline	ergic agonists	(Muscarininc antagonists)			
Direct agonists (prevent breakdown of ACH)	Indirect acting agonists (anticholinesterases)	Natural alkaloids	Synthetic atro		
 Methacholine 	Reversible: Physostigmine,	• Atropine:	Homatropine	1-3 days	

Carbachol Drugs Pilocarpine (1st

line in open angle Isoflurophate glaucoma)

1. Glaucoma (open and closed angle)

ecothiophate, Isoflurophate)

3. To break iris-lens adhesions (in inflammation)

4. in accommodative esotropia الحول (Physostigmine,

2. Counteract action of mydriatics (after fundus examination)

5. Induction of miosis in surgery (Carbachol & Methacholine)

demecarium Irreversible: Ecothiophate,

/-10 days. Scopolamine (hyoscine): 3-7

days.

muscles)

reflex.

(toxic dose).

Cyclopentolate **Tropicamide**

To prevent adhesion in uveitis & iritis

Measurement of refractive error

Mydriasis → due to relaxation of circular

blurred vision, tachycardia, constipation, urinary

• CNS effects: sedation, hallucination, excitation

retention, dryness of mouth, dry sandy eyes, fever

alinavaja antaganista

days 24 hours 6 hours Funduscopic examination of the eye (Passive

Glaucoma (angle closure glaucoma). Tachycardia, Prostate hypertrophy in old patients. Constipation, paralytic ileus. • Cycloplegia (loss of near accommodation) → due to relaxation of ciliary muscles → Loss of light

Bronchial asthma, Peptic ulcer, Coronary vascular disease, C/I Incontinence سلس البول, Intestinal obstruction • Systemic: Lacrimation, salivation, sweating, perspiration, bronchial constriction, urinary urgency, nausea, vomiting, Side and diarrhea. effects • CNS effects: high doses (physostigmine & pilocarpine). • Ocular side effects: diminished vision (myopia), headache, cataract, miotic cysts, and rarely retinal detachment.

USES

Non-selective

agonists

drug of

epinephrine).

Epinephrine.

Dipivefrin (pro-

Drugs acting on sympathetic system

Adrenergic agonists

Selective α_1 agonists

Phenylepherine

Mydriasis (without

cycloplegia),

decongestant

To prevent adhesion in

Decongestant in minor

increase in blood pressure

precipitation of acute angle-

closure glaucoma in patients

allergic hyperemia of eye.

of the eye

uveitis & iritis

May cause significant

Rebound congestion

with narrow angles.

Funduscopic examination

Selective α 2 agonists

Apraclonidine

(eye drops)

aqueous humor, and

of aqueous humor

prophylaxis against

headache, dry

mouth, fatigue,

Letharqy,

bradycardia, and

hypotension.

IOP spiking after

glaucoma laser

procedures.

open glaucoma

treatment.

1 uveoscleral outflow

↓ production of

B blockers

carteolol

drops

betaxolol)

Non-selective: timolol,

Selective β_1 : betaxolol

"cardioselective"

Act on ciliary body to \downarrow

production of aqueous

humor

Given topically as eye

Open angle glaucoma

in patients with

Bronchospasm (less with

arrhythmia; hypotension,

asthmatic patients or

patients with CVS disorders.

• CNS effects (depression,

Cardiovascular (bradycardia,

hypertension

asystole, syncope)

weakness, fatique).

Advantage: can be used

Although they cause mydriasis, they treat <u>only</u> open angle glaucoma by ↑ uveoscleral outflow of aqueous humor



Drug



1 uveoscleral outflow of aqueous humor Used locally as eye drops open angle glaucoma

headache,

arrhythmia, increased

blood pressure

Narrow angles → may

precipitate closed angle

glaucoma.

Side effect

C/I

Flow of Aqueous Humor:

A Closer Look at the Trabecular Meshwork

Drugs used for glaucoma.

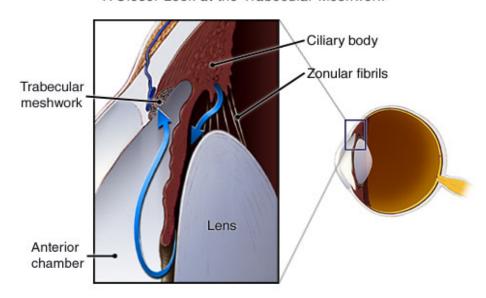
Drugs used for inflammatory conditions.

Drugs used for allergies.

Drugs used in infections of eye.

Drugs for diagnostic purposes.

Drugs used for other diseases in the body producing significant harmful effect on the eye.



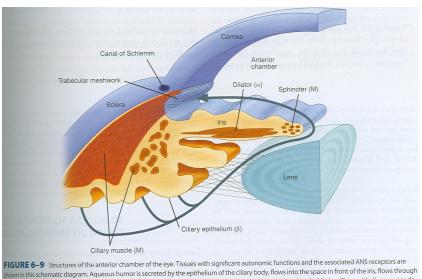
In order to understand the two subtypes of the disease that are the focus of today's case, we must understand the dynamics of aqueous humor production and flow. Disruption of this process can result in elevated IOP and contribute to the pathogenesis of glaucoma.

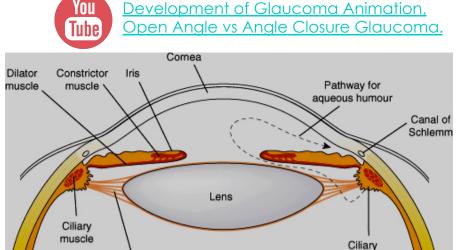
The aqueous humor is secreted by the Ciliary body. Produced by a combination of active transport of ions and ultrafiltration of interstitial fluid.

The fluid flows over the surface of the lens, out through the pupil into the anterior chamber. Flows through the trabecular meshwork into Schlemm's canal and is collected in the scleral veins.

Seeing this flow pattern, you can imagine how problems can occur and result in accumulation of fluid and elevated pressure.







Suspensory

ligaments

The aqueous humor is secreted by the epithelium of ciliary body. Produced by a combination of active transport of ions and ultrafiltration of interstitial fluid. The fluid flows over the surface of the lens, out through the pupil into the anterior chamber. Flows through the trabecular meshwork into Schlemm's canal and is collected in the scleral veins.

Development of angle closure glaucoma and its reversal by miotics

lar meshwork, and exits via the canal of Schlemm (arrow). Blockade of the β adrenoceptors associated with the ciliary epithelium causes de-

osed secretion of aqueous. Blood vessels (not shown) in the sclera are also under autonomic control and influence aqueous drainage.

A. Mydriasis occurs in an eye with narrow iridocorneal angle and the iris makes contact with the lens blocking passage of The aqueous from the posterior to the anterior chamber.

- **B.** Possibly builds up behind the iris which bulges forward and closes the iridocorneal angle thus blocking aqueous outflow.
- C. Miotic makes the iris thin and pushes it away from the lens removing the pupillary block and restoring aqueous drainage.
- A B Miotic

body

- Increase in lacrimation by alpha receptors.
- Increase in aqueous flow by beta receptor by increase the drainage or by decrease the production (beta antagonist can reduce the production because it involve the receptor in blood vessels for this it uses to treat glaucoma.)

Treatment of open angle glaucoma (chronic)

-The problem in open angle in the increase of production of aqueous humor.

Goal: to decrease IOP.

How? 1-Decreasing production of aqueous humor. 2-Increasing outflow of aqueous humor.

- Beta blockers.
- Alpha-2 agonists.
- Carbonic anhydrase inhibitors.

- **Prostaglandins**
- Adrenergic agonists, nonspecific
- Parasympathomimetics.

Prostaglandins and Beta blockers are the most popular

	Carbonic anhydrase inhibitors e.g. acetazolamide (oral), dorzolamide (topical)	Prostaglandin analogues E.g. latanoprost, travoprost			
Mechanism	production of aqueous humor by blocking carbonic anhydrase enzyme required for production of bicarbonate ions (transported to posterior chamber, carrying osmotic water flow).	 increase uveoscleral aqueous outflow. Latanoprost is preferred due to lesser adverse effects. they have replaced beta blockers. -They are used topically as eye drops & once a day. 			
Uses	open angle glaucoma.				
Side Effects	Myopia, malaise, anorexia, Gl upset, headache Metabolic acidosis, renal stone Bone marrow suppression "aplastic anemia" (Usually this side effect happen in case acetazolamide in oral way)	 pigmentation of the iris (heterochromia iridis) Intraocular inflammation Macular edema. 			
Contraindication	Sulfa allergy, pregnancy				

Treatment of narrow closed angle glaucoma (acute)

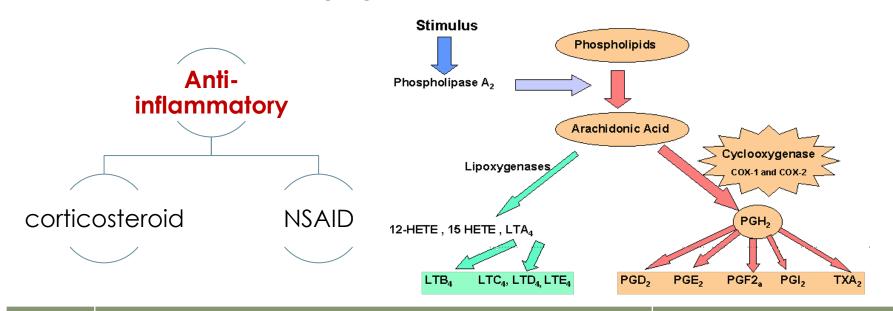
- <u>Acute</u>, <u>painful</u> increases of pressure due to occlusion of the outflow drainage pathway
- Emergency situation that require treatment before surgery (Iridectomy)

The use of drugs is limited to:

- Oral Acetazolamide
- Topical cholinomimetics e.g.: pilocarpine
- Osmotic agents: hypertonic solution (Mannitol, Glycerol).
- Analgesics: pethidine or morphine (for pain).
 - Closed angle glaucoma has very sever pain (acute), the drugs aren't enough for treatment, so we give them to the patient until having the surgery.
 - Osmotic means drugs extracted from sugar like mannitol or glycerol.

	Osmotic agents					
 Can <u>rapidly</u> lower IOP by decreasing vitreous volume. Glycerol 50% syrup, orally (cause nausea, hyperglycemia). Mannitol 20% IV (cause fluid overload and not used in heart failure). 						
Side effects	Diuresis, circulatory overload, pulmonary edema and heart failure, central nervous system effects such as seizure, and cerebral hemorrhage.					
Notes	used only in <u>acute situations</u> to temporarily reduce high IOP until more definitive treatments can be rendered.					

Treatment of narrow closed angle glaucoma (acute).. continue



	Corticosteroids	NSAID
MOA	inhibition of arachidonic acid release from phospholipids by inhibiting phospholipase A2.	inhibition of cyclo- oxygenase
Uses	 1-Topical: E.g. prednisolone, dexamethasone, hydrocortisone. Uses: anterior uveitis, severe allergic conjunctivitis, scleritis, prevention and suppression of corneal graft rejection. 2-Systemic: E.g. prednisolone, cortisone. Uses: posterior uveitis, optic neuritis. 	post-operatively, mild allergic conjunctivitis, mild uveitis, cystoid macular edema, preoperatively to prevent miosis during surgery
Side effects	 Glaucoma, cataract, mydriasis. Suppression of pituitary-adrenal axis. Hyperglycemia, Osteoporosis. Peptic ulcer, Psychosis, susceptibility to infections. 	stinging لاذع
Notes	Side effects: Hypertension, high body weight, inhibition for immune. Contraindication: on diabetic and children (better to be given by inhalation than orally.)	Its mild if I want something strong I give corticosteroid

Harmful drugs for the Eye

1- Drugs that ↑ IOP:

- Mydriatic cycloplegics, tricyclic antidepressants.
- Chronic **steroid** use.
- **2- Cataractogenic drugs:** steroids, heavy metals...
- 3- Drug-induced retionopathies: ethanol, methanol.



4- O2: 40 % for prolonged periods in premature infants causes **Retrolental fiboplasia** (abnormal proliferation of fibrous tissue immediately behind the lens of the eye, leading to blindness) → (Caused by disorganization growth of blood vessels when infants are given O2 in case of having immature lungs).

5- Drugs causing corneal deposits:

- Amiodarone, digitalis, chloroquine (Chloroquine is anti-malarial drug)
- Optic neuropathy (mild decreased vision, visual field defects)
- Corneal keratopathy which is pigmented deposits in the corneal epithelium.
- Digitalis: cardiac failure drug → causes ocular disturbances producing chromatopsia (objects appear yellow) with overdose.
- Mydriasis can be caused by:
 - 1. Adrenergic agonists (cause cycloplegia).
 - 2. Muscarinic antagonist (which cause cycloplegia due to excess relaxing of Ciliary muscle like atropine).
- If alcohol is contaminated with methanol the person will lose his vision. Even when Methanol is drunken once it may cause blindness.

	Local anesthetics	Antibiotics
		 Penicillins, Cephalosporins, macrolides Sulfonamides, Tetracyclines, chloramphenicol Aminoglycosides, Fluoroquinolones, Vancomycin
	 Topical: E.g. propacaine, tetracaine. Removal of corneal foreign bodies Removal of sutures. Examination of patients who cannot open eyes because of pain 	 Conjunctivitis (inflammation of conjunctiva) Keratitis (corneal inflammation) Blepharitis (eye lid inflammation) Endophthalmitis (intraoculatr tissue inflammation). 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 Used intravenously for the treatment of orbital cellulitis e.g. gentamicin, cephalosporin, vancomycin Can be injected intravitrally for the treatment of endophthalmitis
Uses	 Orbital infiltration: e.g. lidocaine, bupivacaine. Peri-bulbar or retro-bulbar cause <u>anesthesia</u> and <u>akinesia</u> for intraocular surgery 	 1.Trachoma infectious disease caused by the bacterium Chlamydia trachomatis can be treated by topical and systemic tetracycline or erythromycin, or systemic azithromycin. 2.Bacterial keratitis (bacterial corneal ulcers) can be treated by topical fortified penicillins, cephalosporins, aminoglycosides, vancomycin, or fluoroquinolones. 3.Bacterial conjunctivitis is usually self limited but topical
	Infiltration anesthetics mean injection	erythromycin, aminoglycosides, fluoroquinolones, or chloramphenicol can be used



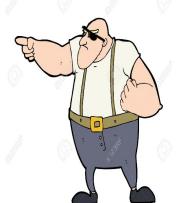
Propacarine



tetracarine

The carine family is well known for being a gang family their sons prop & tetr where known for being so tough that they can take a forgin body out of their eyes !!!!





lido-carine

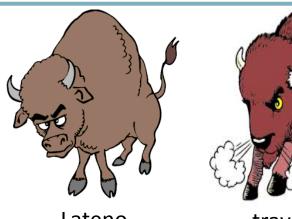


bupivacarine

And they cousins lido & bupiva are way tougher that they lost one of their eyes after injecting themselves right in the eye !!!!!

Hadeel alsalmi

In a Spanish village called prost lived to buffalos lateno & travo people where glad-ins to see their bullfights, and they were so good that they beaten beta Xs matadors group.



Latenoprost



travoprost

After Beta Xs matadors defeat they became hypertensive and the laugh of the city. People started adding lol to their names.





				IIIMI	<i>y</i>		
Drugs acting on parasympathetic system			Drugs acting on sympathetic system				
Cholinergic agonists		Cholinergic antagonists (Muscarininc antagonists)		Adrenergic agonists			
Direct agonists	Indirect acting agonists (anticholinesteras es)	Natural alkaloids	Synthetic atropine substitutes	Non-selective agonists (α_1 , α_2 , β_1 , β_2)	Selective α_t agonists e.g. phenylepherine	Selective α2 agonists e.g. apraclonidine (eye drops)	β blockers
Methacholine, carbachol, pilocarpine	Reversible :Physos tigmine, demecarium irreversible: Ecoshiophate, isoflurophate	Atropine 7-10 days Scopolamine (hyoscine) 3-7 days	Homatropine 1-3 days Cyclopentolat e 24 hour Tropicamide 6 hour	e.g. epinephrine, Dipivefrin (pro- drug of epinephrine). Used locally as eye drops	Mydriasis (without cycloplegia), decongestant	Mechanism: 1 production of aqueous humor, and 1 uveoscleral outflow of aqueous humor	non-selective: timolol, carbeolol Selective β ₀ : betaxolol "cardioselective" Given topically as eye drops
USES: Glaucoma (open and closed angle) Counteract action of mydriatics To break iris-lens adhesions in accommodative esotropia (ecothiophate) Induction of miosis in surpery Open angle glaucoma		USES: To prevent adhesion in uveitis & iritis Funduscopic examination of the eye Measurement of refractive error		Uses: open angle glaucoma Mechanism: 1 uveoscleral outflow of aqueous humor Side Effects: headache, arrhythmia, increased blood pressure	Uses: Funduscopic examination of the eye To prevent adhesion in uveitis & iritis Decongestant in minor allergic hyperemia of eye.	Uses: open glaucoma treatment, prophylaxis against IOP spiking after glaucoma laser procedures.	Uses: open angle glaucoma Mechanism: Act on ciliary body to 1 production of aqueous humor Advantages can be used in patients with hypertension
Contraindications of cholinergic agonists: Pronchial asthma. Protic ulcer. Coronary vascular disease incontinence intestinal obstruction Systemic side effects of cholinergic agonists: Lacrimation, salivation, sweating, perspiration, bronchial constriction, urinary urgency, nausea, vomiting, and diarrhea. CNS effects: high doses (physostigmine & pilocarpine) Ocular side effects: diminished vision (myopia), headache, cataract, miotic cysts, and rarely retinal detachment		Contraindicati antimuscarini Glaucoma (an glaucoma) Tachycardia, P hypertrophy is Constipation, ileus.	c drugs gle closure rostate n old patients.	C/I: in patients with narrow angles as they may precipitate closed angle glaucoma.	Side effects: May cause significant increase in blood pressure Rebound congestion precipitation of acute angle- closure glaucoma in patients with narrow angles.	Side Effects: headache, dry mouth, fatigue, Lethargy, bradycardia, and hypotension.	Side effects Bronchospasm (less with betaxolol) Cardiovascular (bradycardia, arrhythmia; hypotension, asystole, syncope) CNS effects (depression, weakness, fatigue). C/l in asthmatic patients or patients with CVS disorders.



	Treatm	ent of glaucoma			
Treatment of open angle glad	ucoma (chronic)	Treatment of narrow closed angle glaucoma (acute)			
The main goal is to decrease IOP by: Decreasing production of aqueous humor Beta blockers Alpha-2 agonists Carbonic anhydrase inhibitors Increasing outflow of aqueous humor Prostaglandins Adrenergic agonists, nonspecific Parasympathomimetics Prostaglandins and Beta blockers are the most popular		Acute, painful increases of pressure due to occlusion of the outflow drainage pathway emergency situation that require treatment before surgery (Iridectomy) The use of drugs is limited to: Oral Acetazolamide Topical cholinomimetics e.g.: pilocarpine Osmotic agents: hypertonic solution(Mannitol, Glycerol). Analgesics: pethidine or morphine (for pain)			
Carbonic anhydrase inhibitors e.g. acetazolamide (oral), dorzolamide (topical)	Prostaglandin analogues E.g. latanoprost, travoprost	Osmotic agents	Anti inflammatory: Corticosteroids	Anti inflammato ry: NSAID	
Mechanism: ↓ production of aqueous humor by blocking carbonic anhydrase enzyme required for production of bicarbonate ions (transported to posterior chamber, carrying osmotic water flow).	Mechanism: increase uveoscleral aqueous outflow. Latanoprost is preferred due to lesser adverse effects. they have replaced beta blockers. They are used topically as eye drops & once a day.	Mechanism: can rapidly lower IOP by decreasing vitreous volume. Glycerol 50% syrup, orally (cause nausea, hyperglycemia). Mannitol 20% IV (cause fluid overload and not used in heart failure).	Mechanism: inhibition of arachidonic acid release from phospholipids by inhibiting phosphlipase A2	E.g. ketorolac, diclofenac Mechanism: inhibition of cyclo-oxygenase	



1-Which of the following is not a characteristic of eye drops root of administration:

a)The most common

b) Has a long contact time

c) Is has to be used several times a day

2-Which of the following injections is best applied for a patient who was prescribed to acetylcholine for his cataract?

a)Subconjunctival

b)ntravitreal

c)ntracameral

3-Which of the following statements is true regarding systemic administration:

a)Lipid solubility of the drug is inversely proportional to the absorption.

b)Protein binding is inversely proportional to the bioavailability of the drug.

C) Protein binding is inversely proportional to the absorption.

4-A 45 year old asthmatic patient suffering of glaucoma the doctor has given him a drug to resolve all his symptoms -treat-. which of the following is the drug was prescribed for him:

a)Physostigmine

b) Apraclonidine

c)Carteolol

d)Dorzolamide

5-A 53 year old hypertensive female was referred to ophthalmic clinic as she had glaucoma, which of the following drugs works best for her:

a) Selective α 2 agonists

b)Prostaglandins

c) B blockers

6-which of the following is used in accommodative

a)esotropia

b)pilocarpine

c)carbachol

d)Isoflurophate

7-A 60 YO\M whose diabetic for the past 20 years has glaucoma -closed angle - .the doctor prescribed him a drug until he go into the surgery . which of the following is more suitable for him:

a)Hydrocortisone

b)Oral Acetazolamide

c)Glycerol syrup

8-Which of the following is contraindicated for glaucoma

a)Cyclopentolate

b)Physostigmine

c)Latanoprost

9-Which of the following Drugs causing corneal

deposits: a)Chloroquine. 2-с 6-с

b)Pilocarpine c)methanol.

9-a

1-b 5-c

3-c 7-b

4-d 8-a

Good luck! Done by Pharmacology team 434

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