pharmacology
Team 438

MED438
KING SAUD UNIVERSITY

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Neuropsychiatry Block

Pharmacology Team 438

Pharmacology of Drugs Acting on the Eye

Objectives

By the end of the lecture , you should know:

- Outline common routes of administration of drugs to the eye.
- Discuss the pharmacokinetics of drugs applied topically to the eye.
- Classify drugs used for treatment of disorders of the eye.
- Outline ocular toxicity of some drugs.
- Elaborate on autonomic drugs, anti-inflammatory drugs,and drugs used for glaucoma.

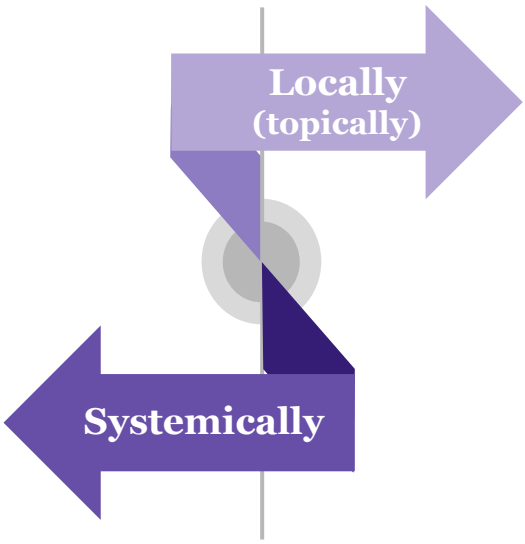
Color index:

Black : Main content
Red : Important
Blue: Males' slides only
Pink : Females' slides only
Grey: Extra info or explanation
Green : Dr. notes

Editing File

How drugs can be delivered to ocular tissue?

- ❖ orally
- ❖ IV



- ❖ Eye drops 
- ❖ Ointment 
- ❖ Eye injections: 
  - Periocular injection
  - Intraocular injection
- ❖ Local administration is:
  - More common.
  - **Pros**: Convenient, Economic, Relatively safe.
  - **Cons** : Compliance, Corneal & conjunctival toxicity.

1) Locally (Topically) :

01 Eye Drops

- most common.
- one drop = 50 µl .
- Their contract time is **low to be used several times.**

02 Ointment

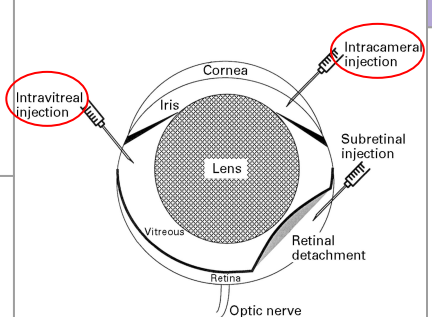
- **Advantage :** Increase the contact time of ocular medication to ocular surface thus **better effect.**
- **Disadvantage :** The drug has to be **high lipid soluble** to have the maximum effect.

Eye injections

03 intraocular Injections

1-intra-cameral[1]**:**
E.g. :
- Intracameral acetylcholine or lidocaine during **cataract surgery**.[2]

2- Intra-vitreal[3]**:**
E.g. :
- Intravitreal antibiotics in cases of **endophthalmitis**.[4]
- Intravitreal steroid in **macular edema**.[5].



Uses	A.D.R
- Anterior segment surgery - Infection - Retinitis	- Retinal toxicity. - Intraocular toxicity. - Corneal toxicity.

1- inside anterior or posterior chamber of the eye.
2- cataract is a clouding of the lens in the eye which leads to a decrease in vision.
3- inside the eye (vitreous humor).
4- an inflammation of the internal coats of the eye.
5- the build-up of fluid in the macula, an area in the center of the retina.

Eye injection (CONT...)

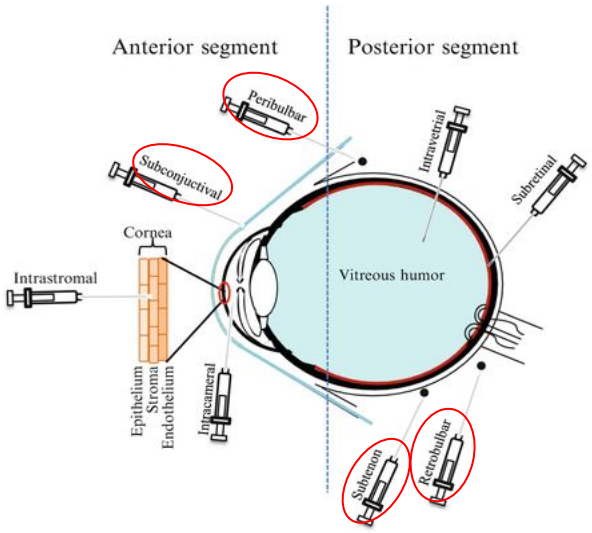
04 periocular Injections

1- Subconjunctival[1]

2- Retrobulbar[2]

3- Peribulbar[3]

4- Subtenon[4]



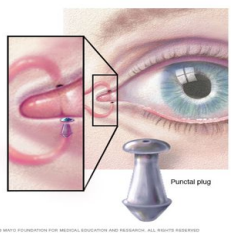
Advantages:
- Reach behind iris-lens diaphragm **better than** topical application.
- bypass the conjunctival and corneal epithelium which is good for **drugs with low lipid solubility (e.g. penicillins).**
- **Steroid** and **local anesthetics** can be applied this way.
- Used for infection of anterior segment and inflammation of uvea (vascular tunic).

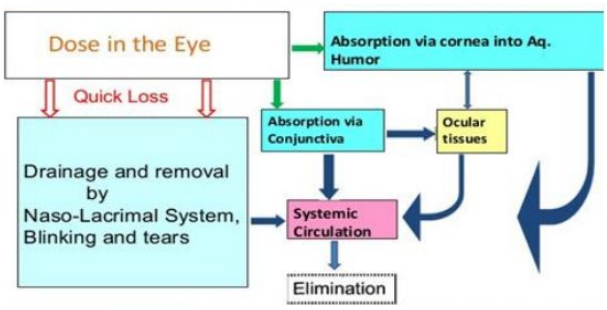
Disadvantages:
- Local toxicity, tissue injury, globe perforation, optic nerve damage.

Pharmacokinetics of topical drugs:

Absorption

The rate of absorption is determined by :
- **Drug residence time :**
the time drug remains in cul-de-sac[5], tear.
It can be prolonged by
plugging tear ducts or change formulation.
- **Metabolism :**
Significant biotransformation takes place in the eye.
Esterases activate pro-drugs, e.g.:
- Dipivefrin →(adrenaline)
- Latanoprost →(PGF2α)
- **Elimination :**
by nasolacrimal drainage or binding to tear protein.
- **Diffusion :** across cornea & conjunctiva





Distribution

- After corneal absorption, the drug accumulates in the aqueous humor, intraocular structures or systemically distributed.
- Melanin binding prolongs the effect of α agonists in patients with dark pigmented iris.
- Chloroquine binds to retinal pigment →↓ visual acuity.

2) systemically (Orally \ IV) :

Factors that can control systemic drug penetration into ocular tissue are :

1. **Lipid solubility of the drug:** more penetration with high lipid solubility.
2. **Protein binding :** more effect with low protein binding.[6]
3. **Eye inflammation :** more penetration with ocular inflammation.

1- beneath the conjunctiva.
2- behind the eyeball.
3- above and below the orbit (orbit is the cavity of the skull in which the eye is situated).
4- Used to describe injections through the membrane covering the muscles and nerves at the back of the eyeball.
5- In anatomy : cavity that is closed at one end. 6- remember: low protein binding —> short duration of action and vice versa

Ocular drugs

1. **Autonomic drugs**
   - Miotics
   - Mydriatics
   - Cycloplegics
2. **Antiglaucoma Drugs**
3. **Anti-inflammatory drugs :**
   - Steroids
   - NSAIDs
4. **Chemotherapeutics :**
   - Antibacterial
   - Antifungal
   - Antiviral
   - Antimitotic
5. **Local anesthetics**
6. **Ocular lubricants**

Autonomic drugs

A) Parasympathetic drugs

Ocular actions of cholinergic drugs

1- Contraction of the pupillary sphincter muscle **(meiosis)**.

2- Contraction of the ciliary muscle **(accommodation for near vision)**.

3- Decrease in intraocular pressure ↓ **IOP.**

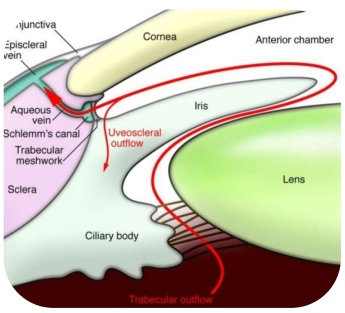
4- Conjunctival Vasodilation

5- Increased lacrimation

6 - increases aqueous outflow through the trabecular meshwork into canal of Schlemm by ciliary muscle contraction.

How does parasympathetic drugs causes decreasing in IOP?

- The aqueous humor is secreted by the epithelium of ciliary body.
- It's 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 (Drainage by) :
1- the trabecular meshwork into Schlemm's canal.
2-uveoscleral drainage is collected in the scleral veins.

Parasympathomimetics produce contractions of circular muscles of iris thus pulling ciliary muscles away from the trabecular meshwork and Schlemm's canal **thus** facilitating drainage and reducing intraocular pressure.

Cholinergic agonists

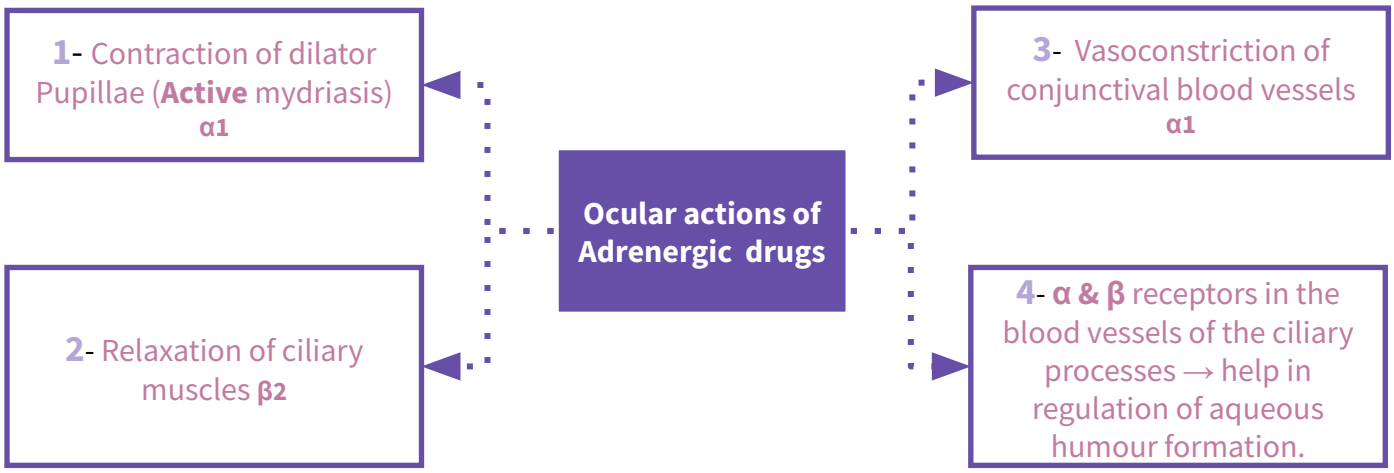
Direct agonists				
Drug	**Methacholine**	**Carbachol**	**Ach**	**Pilocarpine**
Specific Indications	- Induction of miosis in surgery. - Open angle glaucoma.			- Open angle glaucoma.[1]
Indirect Agonists (anticholinesterases)				
Type	**Reversible**		**Irreversible (phosphate ester)**	
Drug	**Physostigmine**	**Demecarium**	**Isofluorophate**	**Echothiophate**
Specific Indications	- Glaucoma. - Accommodative esotropia.[2] ⟶ **echothiophate + physostigmine**. - In lice infestation of lashes.⟶ **physostigmine.**			
Both: Direct & Indirect				
Indications	- Glaucoma (open & closed angle). - To break iris-lens adhesions. [6]		- Counteract action of mydriatics.	
A.D.R	**Ocular:** • Diminished vision (myopia). • Headache			

Cholinergic antagonists (Muscarinic)

Drug	**Natural alkaloids**		**Synthetic atropine substitutes**		
	Atropine	**Scopolamine (Hyoscine)**	**Homatropine**	**Cyclopentolate**	**Tropicamide**
Duration of Effect	7-10 days	3-7 days	1-3 days	24 hours	6 hours
Actions	- **Passive mydriasis**[3] due to relaxation of circular muscles. - **Cycloplegia** (loss of near accommodation) due to relaxation of ciliary muscle. - Loss of light reflex. - Increased IOP - Decreased lacrimal secretion ⟶ sandy eye.				
Clinical uses	- To prevent adhesion in uveitis & iritis. - Funduscopic examination of the eye. - Measurement of refractive error[4] ⟶ (myopia, hyperopia).				
C.I	- Glaucoma (angle closure glaucoma).[5]				

1- The drug of choice in acute attack (closed or open glaucoma). 2- نوع من الحول
3- passive = the mydriasis occurred due to the paralysis of the circular muscles (and not the contraction of radial muscles).
4- problems with light focusing on the retina due to the shape of the eye.
5- Because there is mydriasis⟶ which decreases the angle of filtration ⟶IOP rises dangerously ⟶ acute attack .
6- inflammation caused by iritis can lead to adhesion between the iris and the lens.

B) Sympathetic drugs



Adrenergic agonists

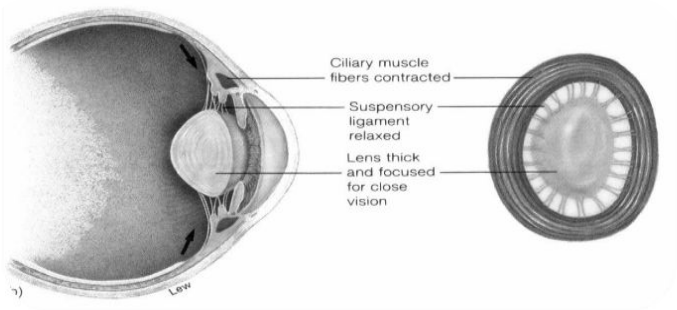
Drug	Selective α2 agonists	Selective α1 agonists	Non-selective agonists (α1 , α2 , β1 , β2)
	Apraclonidine	**Phenylephrine**	**-Dipivefrin** *(pro-drug of epinephrine)* **-Epinephrine**
M.O.A	- ↓ production of aqueous humor. - ↑ uveoscleral outflow of aqueous humor.	- Active mydriasis due to contraction of radial muscles of the eye **(without cycloplegia)**	- ↓ aqueous humor production through vasoconstriction of ciliary body blood vessels. [1] - ↑ uveoscleral outflow of aqueous humor.
Uses	- Open angle glaucoma - Prophylaxis against IOP spiking after glaucoma laser procedures.	- Fundoscopic examination of the eye. - To prevent adhesion in uveitis & iritis. - Decongestant in minor allergic hyperemia of eye.	- Used locally[2] as eye drops → in Open angle glaucoma.
A.D.R	- Bradycardia. - Hypotension.	- May cause significant increase in blood pressure. - Rebound congestion.	- Headache. - Arrhythmia. - Increased blood pressure.
C.I	-	- in patients with narrow angles as they may precipitate closed angle glaucoma.	

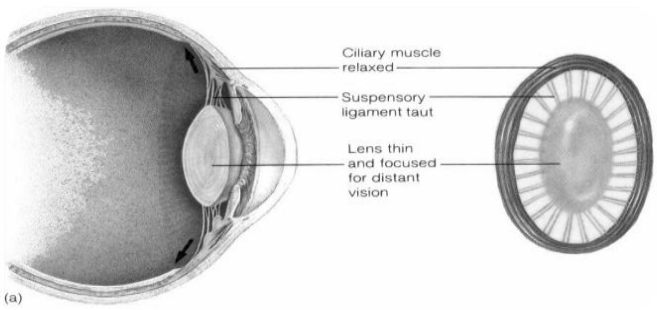
1- according to the females doctor: it's the main function.
2 - to minimize the ADRs.

β Blockers

Drug	Selective β1 (cardio-selective)	Non-selective	
	Betaxolol	Carteolol	Timolol
M.O.A	Act on epithelium of ciliary body to ↓ production of aqueous humor.		
Route of Administration	Given topically as eye drops.		
Advantages	-Can be used in patients with hypertension & ischemic heart disease. -Betaxolol is not causing bronchospasm		
Uses	Open angle glaucoma.[1]		
A.D.R	Ocular Irritation.		

Accommodation for near/far vision :





Eye		Sympathetic N.S. (far vision)	Parasympathetic N.S. (near vision)
Iris:	- radial muscle	Contraction (Mydriasis) (α1) Active mydriasis	No effect
	- circular muscle	No effect	Contraction (miosis) (M3)
Ciliary muscle		Relaxation (β2)	Contraction (M3)
Lens		Thin, more flat	Thick, more convex
Suspensory ligaments		Contraction	relaxation
Conjunctival blood vessels		Conjunctival Vasoconstriction and decongestion of blood vessels.	Conjunctival Vasodilatation and congestion of blood vessels.

1 - β-adrenergic blocker timolol, are effective in treating chronic glaucoma but are not used for emergency lowering of intraocular pressure.

Treatment of open angle glaucoma (chronic)

The main goal is to decrease IOP by:

1 **Decreasing production of aqueous humor**

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

2 **Increasing outflow of aqueous humor.**

- **Prostaglandins.**
- **Adrenergic agonists (nonspecific).**
- **Parasympathomimetics.**

- **Prostaglandins and Beta blockers are the most popular**[1]

Drug	Prostaglandin analogues		Carbonic anhydrase inhibitors	
	Latanoprost	Travoprost	Acetazolamide (oral)	Dorzolamide (topical)
M.O.A	- ↑ uveoscleral aqueous outflow. - They have replaced beta blockers.[2] - They are used topically as eye drops & once a day.		- ↓ production of aqueous humor by blocking carbonic anhydrase enzyme required for production of bicarbonate ions ⟶ (transported to posterior chamber, carrying osmotic water flow).	
Uses	open angle glaucoma			
A.D.Rs	- Pigmentation of the iris (heterochromia iridis) - **Latanoprost** is preferred due to lesser adverse effects.		- Myopia[3], malaise, anorexia, GI upset, headache, Metabolic acidosis, & renal stone.	
C.I	----------		- Sulfa allergy - Pregnancy - Digitalis users.	

Treatment of narrow closed angle glaucoma (acute)

- Acute, painful increases of intraocular pressure due to occlusion of the outflow drainage pathway.[4]
- emergency situation that require treatment before surgery **(Iridectomy)**.

The use of drugs is limited to :

- **Osmotic agents :** Hypertonic solution (**Mannitol**, **Glycerol**).
- **Analgesics :** **Pethidine** or **morphine** (for pain).
- Oral **Acetazolamide**
- **Topical cholinomimetics:** e.g. **Pilocarpine**

1-According to dr.hanan prostaglandin is the first choice and beta blocker is the second choice
2- Better than beta blockers because it has a long duration.
3- Dorzolamide will only cause myopia because it's administered topically.
4- The main treatment is surgery but medications are given temporarily until a surgery is scheduled.

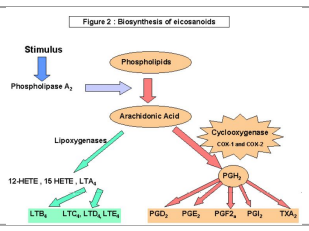
Osmotic agents

(dehydrating agent) → Systemic

M.O.A	- IV infusion of hypertonic solution (**Mannitol**, **Glycerol**). - Can rapidly ↓ IOP by ↓ vitreous volume prior to anterior surgical procedures. - **Glycerol** 50% syrup, orally (cause : nausea, hyperglycemia).[1] - **Mannitol** 20% IV (cause : fluid overload and not used in heart failure).
Uses	Used only in acute situations to temporarily reduce high IOP until more definitive treatments can be rendered. (short term management)
A.D.R	- Diuresis, circulatory overload, pulmonary edema , heart failure -CNS effects such as seizure, and cerebral hemorrhage.

Anti-inflammatory drugs

A) Corticosteroids

Drug	Systemic	Topical
	Prednisolone, Cortisone	**Prednisolone, Dexamethasone, Hydrocortisone**
Uses	- **posterior** uveitis. - optic neuritis.	- **anterior** uveitis. - severe allergic conjunctivitis. - scleritis. - prevention and suppression of corneal graft rejection. - postoperatively.
M.O.A	- Inhibition of arachidonic acid release from phospholipids by inhibiting phospholipase A2	
A.D.Rs	- Glaucoma, cataract, increase IOP - Skin atrophy. - Secondary infection. - Delayed wound healing.[2]	

B) NSAID

Drug	Flurbiprofen	Diclofenac	Ketorolac
Uses	- Pre-operatively to prevent miosis[3] during cataract surgery.	- postoperative inflammation. - mild allergic conjunctivitis. - mild uveitis.	- Cystoid macular edema occurring after cataract surgery.
M.O.A	- COX (cyclo-oxygenase) inhibitor.		
A.D.R	- Stinging, sterile corneal melt & perforation.[4]		

1- contraindicated in diabetic patients.
2- healing is slow because it is an immune suppressor.
3- Because they inhibit prostaglandins which causes miosis without the action of cholinergic.
4- because they dissolve keratin.

Sildenafil :
Causes a bluish haze & causing light sensitivity.
Because it Inhibits PDE5 in the corpus cavernosum to achieve penile erection +inhibits PDE6 which controls the level of cyclic GMP in the retina→ seeing a bluish haze & causing light sensitivity

Amiodarone:
- Pigmented deposits of cornea.
- Optic neuropathy.

Chloroquine :
Retinopathy

Ethambutol :
optic neuropathy characterized by gradual Progressive central scotomas[1] and vision loss.

Drugs causing corneal deposits

digitalis
(cardiac failure drug) :
ocular disturbances & **chromatopsia** with overdose (objects appear yellow).

Steroids :
cataract formation, elevated IOP & glaucoma.

Phenothiazines :
Brown pigmentary deposits in the cornea, conjunctiva & eyelid.

Summary

Indications	Drugs
Open angle glaucoma	Direct and Indirect Cholinergic agonists, Selective α2 agonists, Non-selective agonists, β Blockers, Carbonic anhydrase inhibitors, Prostaglandins.
closed angle glaucoma	Direct and Indirect Cholinergic agonists, Oral Acetazolamide, Osmotic agents, Analgesics (for pain).
Fundoscopic examination of the eye	Cholinergic antagonists, Selective α1 agonists, Non-selective agonists.
To prevent adhesions in inflammatory conditions	Direct and Indirect Cholinergic agonists, Cholinergic antagonists, Selective α1 agonists, Non-selective agonists.

1- Central scotoma is an area of depressed vision that corresponds with the point of fixation and interferes with central vision.

Quiz

MCQ

1- Rate of absorption of a topical drug to the eye is determined by _____.

A- Metabolism. B- Elimination.

C- Time of the drug staying in clu-de-sac. D- All above .

2- A patient has open angle glaucoma. After a while of taking medication, she was not able to see while driving. What is the drug that could cause myopia as a side effect ?

A- Carbachol. B- Apraclonidine.

C- Timolol. D- Acetazolamide.

3- A 60 Years old male whose diabetic for the past 20 years has closed angle glaucoma. 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- Mannitol D- Prednisolone

4- Topical corticosteroids (E.g. prednisolone) is used for :

A- Anterior uveitis. B- Severe allergic conjunctivitis.

C- Prevention of corneal graft rejection. D- All above .

5- which of the following is not used in open angle glaucoma :

A- Carbachol. B- Atropine.

C- Timolol. D- Demecarium.

SAQ

Q1- A patient with heart failure history and using digitalis for it. Recently he was diagnosed with open angle glaucoma. What is the drug class will be contraindicated in this case ?

Q2,3,4 - A 53 year old female was referred to ophthalmic clinic as she had open angle glaucoma.

Q2- mention one drug for her condition ?

Q3- what is the mechanism of action of this drug ?

Q4 - if she had hypertension, what is the best drug class for her condition ?

Q5- mention 3 drugs that cause corneal deposition ?

Answers:

MCQ

Q1	D
Q2	A&D
Q3	C
Q4	D
Q5	B

SAQ

Q1	Carbonic anhydrase inhibitor
Q2	Latanoprost
Q3	↑ uveoscleral aqueous outflow
Q4	β Blockers
Q5	Amiodarone, Phenothiazines, Sildenafil

pharmacology

Team 438

Good Luck , Future Doctors!

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Share with us your ideas !