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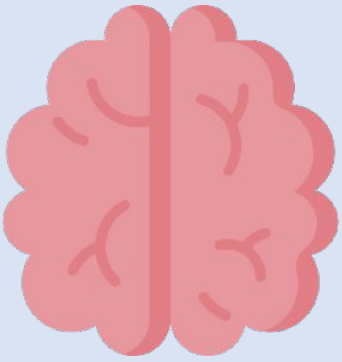
Pharmacology 439
MED439



Neuropsychiatry Block

Pharmacology Team 439

Color index:

Main Text

Important

Dr's Notes

Female Slides

Male Slides

Extra

Pharmacology of Drugs Acting on the Eye

Objectives:

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

Editing file

Effect of sympathetic and parasympathetic on the eye

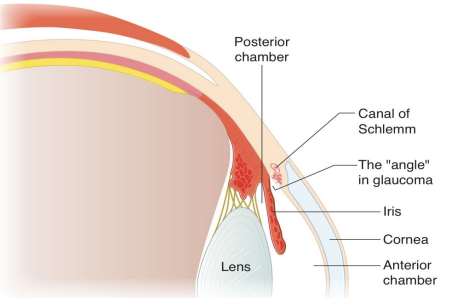
Eye		Sympathetic N.S.	Parasympathetic N.S
Overview		a1: Mydriasis a2: Decrease aqueous humor production B1: Focus on distant objects B2: Increase aqueous humor production	M3: Miosis Focus on near objects
Iris:	-Radial muscle	Contraction (Mydriasis) (α1) active mydriasis	No effect
	-Circular muscle	No 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 Vasodilation and congestion of blood vessels.

Glaucoma

Helpful video

Open-angle glaucoma	Closed-angle glaucoma
Open-angle glaucoma is a chronic condition with increased intraocular pressure (IOP) due to decreased reabsorption of aqueous humor. It leads to progressive (painless) visual loss and, if left untreated, blindness. IOP is a balance between fluid formation and its drainage from the globe.	Closed-angle glaucoma is an acute (painful) or chronic (genetic) condition with increased IOP due to blockade of the canal of Schlemm.
Strategies in drug treatment of glaucoma include the use of beta blockers to decrease formation of fluid by ciliary epithelial cells and the use of muscarinic activators to improve drainage through the canal of Schlemm.	Emergency drug management prior to surgery usually involves cholinomimetics, carbonic anhydrase inhibitors, and/or mannitol.

The aqueous humor is a transparent, watery fluid that is secreted by the ciliary epithelium into the posterior chamber and then flows through a narrow space between the front of the lense and the back of the iris through the pupil to the anterior chamber, from there the fluid flows out of the eye through the trabecular meshwork which acts like a drain and this allows the fluid to go down into a circular channel called the canal of schlemm -> veins
In glaucoma part of this aqueous humor drainage pathway becomes partially or completely obstructed



Anatomy of of the the Eye Irido-Corneal Angle Where Aqueous Humor Is Recirculated

How drugs can be delivered to ocular tissue?

Locally (topically) ◀ ▶ systematically

1) **Eye drops** (must be sterile, isotonic, and viscous)
2) **Ointment**
3) **Eye injections:**
   - Periocular injection (around)
   - Intraocular injection (inside)

Local administration is:
- More common
- Pros: Convenient, Economic, Relatively safe
- Cons: Compliance*, Corneal & conjunctival toxicity

- ❖ Orally
- ❖ IV

*How much the patient stick to the dr's advices.

Locally (Topically)

1- Eye drops

- Most common
- One drop = 50 µ
- Their contact time is low
- they're needed to be used several times

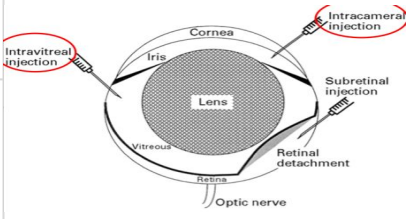
2- Ointment

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

3- Eye Injection

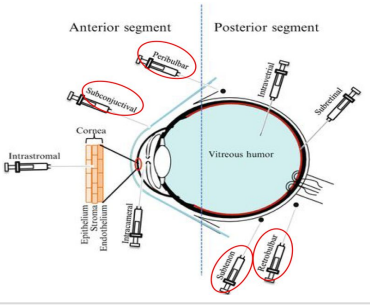
Intraocular Injection

	Intra-cameral	Intra-vitreal
Uses	Acetylcholine or lidocaine during cataract surgery. or antibiotic in the case of endophthalmitis	- Antibiotics in cases of endophthalmitis. - Steroid in macular edema. (a complication of diabetes)
	Anterior segment surgery - infections and retinitis	
A.D.R	Retinal/Corneal toxicity	



Periocular Injections

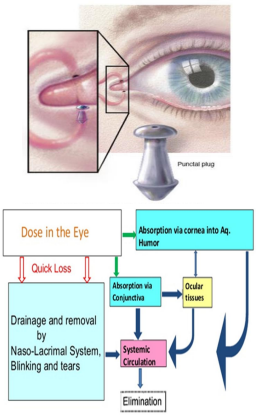
	Subconjunctival	Retrobulbar	Peribulbar	Subtenon
Advantages	- Reach behind iris-lens diaphragm better than topical application - Steroid and local anesthetics can be applied this way - Bypass the conjunctival and corneal epithelium which is good for drugs with low lipid solubility (e.g. penicillins) - For infection of anterior segment and inflammation of uvea			
Disadvantages	Local toxicity, tissue injury, globe perforation, optic nerve damage			



Pharmacokinetics of topical drugs*

*Female slides

Absorption	The rate of absorption is determined by : **Drug residence time :** It can be prolonged by change formulation or plugging tear ducts **Metabolism**: Significant biotransformation takes place in the eye Esterase **Elimination:** By nasolacrimal drainage or binding to tear protein Or by **Diffusion:** across cornea & conjunctiva to systemic circulation.
Distribution	- After corneal absorption, the drug accumulates in the aqueous humor, intraocular structures or systematically distributed - Melanin binding prolongs the effect of a agonists in patients with dark pigmented iris - Chloroquine binds to retinal pigment →↓visual acuity



Systemically (Oral/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 (not bound → can go anywhere)
3. **Eye inflammation:** more penetration with ocular inflammation

Ocular drugs

- **Autonomic drugs:**
  - Miotics
  - Mydriatics
  - Cycloplegics
- **Antiglaucoma Drugs**
- **Ocular lubricants**
- **Chemotherapeutics:**
  - Antibacterial
  - Antifungal
  - Antiviral
  - Antimitotic (Anti cancer)
- **Local anesthetics**
- **Anti-inflammatory** drugs:
  - Steroids
  - NSAIDs

Autonomic drugs

A) parasympathetic drugs

1- Contraction of the pupillary sphincter muscle (circular muscle of iris) (miosis)

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

3- Decrease in intraocular pressure ↓ IOP
By increasing aqueous humor drainage not by decreasing its production

Ocular actions of cholinergic drugs

4- Increased lacrimation
By activating m3 receptors in the lacrimal gland

5- Conjunctival Vasodilation

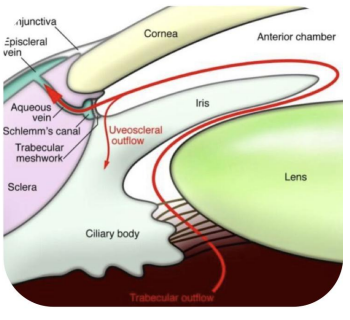
6- Increase in aqueous outflow through the trabecular meshwork into canal of Schlemm by ciliary muscle contraction.

How does parasympathetic drugs causes decreasing in IOP?*

*Female slides

- 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 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.**

- Aqueous humor delivers glucose, O2 to inadequately vascularized areas of the eye (especially the lens).
- Aqueous humor has bicarbonate.
- Drainage of aqueous humor depends on :
  1- Open canal of schlemm.
  2- Wide angle of filtration.
- Iris and ciliary body control drainage by affecting the angle of filtration.
- Contraction of iris & ciliary body (because it contracts away from angle of filtration)-> wider angle of filtration.
- Miosis -> ↓ eye pupil (because of contraction of iris -> wide angle of filtration -> ↑ drainage.
- Mydriasis -> narrow angle of filtration.



Cholinergic agonists

Direct agonists				
Drug	methacholine	Carbachol	Ach*	pilocarpine
Specific Indications	- Induction of miosis in surgery - Open angle glaucoma			Open angle glaucoma
Indirect acting agonists (anticholinesterases) → prevent acetylcholine breakdown				
Type	Reversible		Irreversible	
Drug	Physostigmine	Demecarium	Isoflurophate	Ecothiophate
Specific Indications	- Glaucoma - Accommodative esotropia → Echothiophate + Physostigmine + Isoflurophate (Accommodative esotropia occur in far sighted patients, where they make huge effort to accommodate for near vision, until there eyes get crossed to the opposite direction نوع من الحَوَل) - In lice infestation of lashes → Physostigmine			
Both : Direct & Indirect				
Indications	- Counteract action of mydriatics - To break iris-lens adhesions (treated with any drug that causes contraction of iris muscle i.e. mydriatic & miotic drugs) - Glaucoma (open and closed angle) ➔ Closed angle glaucoma (problem in drainage of aqueous humor due to closed canal of narrow angle of filtration) → only treatment is surgery but medications can be given until day of surgery. ➔ Open glaucoma (due to extra production of aqueous humor)->can be treated with medications.			
A.D.A	**Ocular**: - Diminished vision (myopia) - Headache			

*Boys slides only but it was mentioned by the Female doctor

Cholinergic (Muscarinic) antagonists

Drug	**Natural alkaloids**		**Synthetic atropine substitutes**		
	Atropine	**Scopolamine (hyoscine)**	**Homatropine**	**Cyclopentolate**	**Tropicamide**
Duration of Effect	7-10 days (long duration of action)	3-7 days	1-3 days	24 hour	6 hours
Actions	- Passive Mydriasis due to relaxation of circular muscles - **Cycloplegia** (loss of near accommodation) due to relaxation of ciliary muscles - Loss of light reflex **- Increased IOP** - Decrease Lacrimal secretion →sandy eye				
Clinical uses	- Funduscopic examination of the eye - To prevent adhesion (of iris to lens) in uveitis & iritis (here sympathomimetic drugs, parasympathomimetic drugs and muscarinic antagonist can be used) - Measurement of refractive error → (myopia, hyperopia) (Accommodation disorder)				
C.I	Glaucoma (angle closure glaucoma)				

B) Sympathetic drugs

1- Contraction of dilator Pupillae (radial muscle of iris)
(Active mydriasis)
α1

3- Vasoconstriction of conjunctival blood vessels
α1
(solves hyperemia)

Ocular actions of Adrenergic drugs*
*Female slides

2- Relaxation of ciliary muscle
β2

4- **α & β** receptors in the of blood vessels of the ciliary processes → help in regulation of aqueous humour formation.

- Agonists of **β** increase aqueous humor synthesis.
- Beta blockers decrease aqueous humor synthesis.

- Any parasympathomimetic is used in closed & open glaucoma.
- Any sympathomimetic is contraindicated in closed glaucoma.

Adrenergic agonists

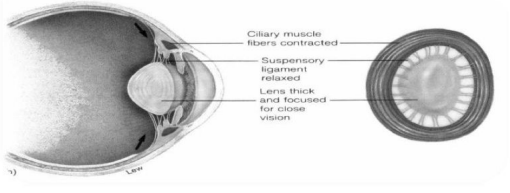
Drug	Selective a2 agonists (sympatholytic)	Selective a1 agonists	Non-selective agonists (a1,a2,β1,β2)
	Apraclonidine	**Phenylephrine**	**- Dipivefrin** (pro-drug of epinephrine) **- Epinephrine**
M.O.A	- ↓ production of aqueous humor. (Does not affect the outflow) - ↑ uveoscleral outflow of aqueous humor.	- Active mydriasis due to contraction of radial muscles of the eye **(without cycloplegia).** - Doesn't affect accommodation of near vision. (Cycloplegia is the paralysis of the ciliary muscle of the eye)	- ↓ aqueous humor production through vasoconstriction of ciliary body blood vessels. - ↑ uveoscleral outflow of aqueous humor.(i.e., fluid flows through the ciliary muscles and into the suprachoroidal space)
Uses	- Open angle glaucoma. - Prophylaxis against IOP spiking after glaucoma laser procedures.	- Fundoscopic examination of the eye. - To prevent adhesion in uveitis & iritis. - Ocular decongestant in minor allergic hyperemia of eye (by vasoconstriction).	- Used locally as eye drops → in open angle glaucoma.
A.D.R	- Headache. - Bradycardia. - Hypotension.	- May cause significant increase in blood pressure. - Rebound congestion.	- Headache. - Arrhythmia. - Increased blood pressure.
C.I	- hypersensitivity to apraclonidine - Systemic clonidine - In patients receiving monoamine oxidase inhibitors	- In patients with narrow angles as they may precipitate closed angle glaucoma.	

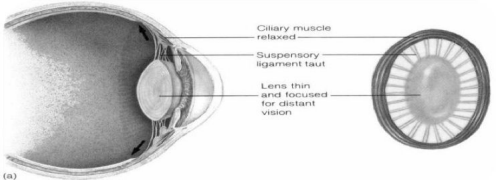
β Blockers

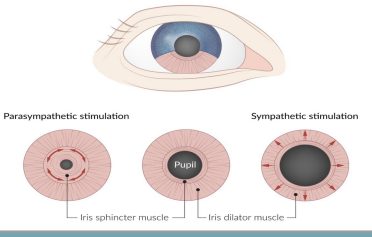
Drug	Selective β1 (cardio-selective)	Non-selective	
	Betaxolol (important)	**Carteolol**	**Timolol** (important)
M.O.A	Act on epithelium of ciliary body (epithelium) to ↓ production of aqueous humor.		
Route of Administration	Given topically as eye drops.		
Advantages	- Can be used in patients with hypertension & ischemic heart disease. - **Betaxolol** doesn't cause bronchospasm		
Uses	Open angle glaucoma (because involved in aqueous humor production)		
A.D.R	Ocular Irritation. Systemic effects if used for a long period ex. bronchoconstriction.		
C.I	**Asthma**, COPD, heart block.		

Accommodation for near/far vision*

*Female slides







Eye		Sympathetic N.S. (far vision)	Parasympathetic N.S. (near vision)
		& by drugs that cause loss of near vision	Accommodation of near vision is related to ciliary body and suspensory ligaments and unrelated to miosis and mydriasis.
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 (always opposite to what happens to ciliary muscle)		Contraction	Relaxation
Conjunctival blood vessels		Conjunctival Vasoconstriction and decongestion of blood vessels.	Conjunctival Vasodilation and congestion of blood vessels.

Treatment of open angle glaucoma (chronic)*

*لأن المريض ممكن يتعايش مع المرض إذا أخذ أدوية

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 (non specific). because they increase uveoscleral flow.
- Parasympathomimetics.

- **#1 Prostaglandins and #2 Beta blockers are the most popular.**

Drug	Carbonic anhydrase inhibitors		Prostaglandin analogue	
	Acetazolamide (oral)	Dorzolamide (topical)	Latanoprost (Topical)	Travoprost
M.O.A	- ↓Production of aqueous humor by blocking carbonic anhydrase enzyme required for production of bicarbonate ions → (transported to posterior chamber, carrying osmotic water flow).		- ↑Uveoscleral aqueous outflow (by vasodilation). - They have replaced beta blockers. - They are used topically as eye drops & once a day.	
Uses	open angle glaucoma			
A.D.R	- Ocular effects: Myopia, malaise, - Anorexia, GI upset, headache, metabolic acidosis & renal stones.		- Pigmentation of the iris (heterochromia iridis) (Becomes darker) - **Latanoprost** is preferred due to lesser adverse effects.	
C.I	- Sulfa allergy - Pregnancy (crosses placenta and causes side effects in baby) - Digitalis users (induce hypokalemia)		hypersensitivity	

Treatment of narrow closed angle glaucoma (acute)

- closed angle glaucoma is: acute, painful increases of intraocular pressure due to occlusion of the outflow drainage pathway.
- Emergency situation that require treatment before surgery (Iridectomy).

The use of drugs is limited to :

- **Osmotic agents** (Dehydrating agents)**:** Hypertonic solution (Mannitol, Glycerol).
- **Analgesics:** Pethidine or morphine (for pain). We don't use NSAIDs
- **Oral:** Acetazolamide
- **Topical cholinomimetics:** E.g. Pilocarpine

Osmotic agents

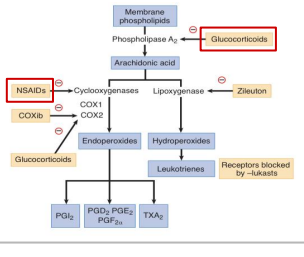
(dehydrating agent) → Systemic

M.O.A	- Dehydrate vitreous body which reduce IOP prior to anterior surgical procedures - IV infusion of hypertonic solution (**Mannitol, Glycerol**). - Can **rapidly** ↓ IOP by ↓ vitreous volume prior to anterior surgical procedures. - **Glycerol** 50% syrup, orally - **Mannitol** 20% IV
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 **(important)**, pulmonary edema, heart failure - CNS effects such as seizure, and cerebral hemorrhage. - **Glycerol** (cause: nausea, hyperglycemia, diarrhea). - **Mannitol** (cause: fluid overload, not used in heart failure).

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				
Ocular A.D.R	- Glaucoma, cataract, increase IOP - Skin atrophy. - Secondary infection. Due to immunosuppression - Delayed wound healing.				



B) NSAID

Drug	Flurbiprofen	Diclofenac	Ketorolac
Uses	- Pre-operatively to prevent miosis during cataract surgery. (eye surgery is trauma to the eye → inflammatory mediators one of which is prostaglandins are released leading to miosis and hyperemia).	- Postoperative inflammation. (to ↓ the inflammation caused by the surgery). - Mild allergic conjunctivitis. - Mild uveitis.	- Cystoid macular edema occurring after cataract surgery. - Cystoid macular edema is a multi cyst like structures which are fluid filled and take place in the macula -(in this case we can use NSAID or corticosteroids).
M.O.A	- COX (cyclo-oxygenase) inhibitor.		
A.D.R	- Stinging, sterile corneal melt & perforation.Corneal melt is an ophthalmological condition in which corneal epithelium is lost accompanied by thinning of the corneal stroma caused by losing corneal collagen, leading to perforations		

Drugs causing corneal deposits

1

Amiodarone:

- Pigmented deposits of cornea.
- Optic neuropathy.

Chloroquine (antimalarial drug)**:**

- Retinopathy

2

Digitalis (cardiac failure drug) :

ocular disturbances & **chromatopsia** with overdose (objects appear yellow).

3

Phenothiazines:

Brown pigmentary deposits in the cornea, conjunctiva & eyelid.

4

Steroids:

cataract formation, elevated IOP & glaucoma.

5

Ethambutol (Anti-TB)**:**

optic neuropathy characterized by gradual Progressive vision loss and central scotomas.

Scotoma: the inability to report the presence of targets of specific size and luminance in various portions of the visual field.

6

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.

Summary

Indicator	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 conditions agonists, Non-selective agonists.

MCQs

*red: Female doctor quiz

Q10: If an ophthalmologist wants to dilate the pupils for an eye examination, which drug/class of drugs is theoretically useful?			
A- Muscarinic receptor activator (agonist)	B-Muscarinic receptor inhibitor (antagonist)	C-Pilocarpine	D- Neostigmine
Q11: Which of the following drugs is commonly used topically in the treatment of glaucoma?			
A- Esmolol	B-Timolol	C-Silodosin	D-Yohimbine
Q3: You are reviewing a 73-year-old man with multiple cardiac problems. He is currently taking ramipril, metoprolol, furosemide, amiodarone and aspirin. Over the past few months he has noted problems with night glare and his optician has diagnosed corneal microdeposits. Which of the following drugs in his regime is most likely to be responsible?			
A- Amiodarone	B-Aspirin	C-Furosemide	D-Metoprolol
Q4: Which of the following cholinomimetics is commonly used in the treatment of glaucoma?			
A- Pilocarpine	B- Lobeline	C- Acethylcholine	D- Neostigmine
Q5: A 54-year-old woman recently diagnosed with open-angle glaucoma was prescribed topical timolol. Two weeks later, intraocular pressure was decreased but was still above the normal value. The ophthalmologist decided to add a topical drug that acts by decreasing aqueous humor production. Which of the following drugs was most likely prescribed as the second drug?			
A- Pilocarpine	B-Carbachol	C-Latanoprost	D-Dorzolamide
Q6: A 57-year-old Black woman, recently diagnosed with closedangle glaucoma, was scheduled for iridotomy. Which of the following agents was most likely given intravenously before and after surgery to reduce intraocular pressure?			
A- Furosemide	B-Triamterene	C-Mannitol	D-Homatropine
Q7: parasympathetic agonist reduces intraocular pressure			
A- true	B- false	C-	D-
Q8: which one of the following has the longest duration of action on the eye?			
A- Homatropine	B- Cyclopentolate	C- Tropicamide	D- Atropine
Q9: which one of the following acts by blocking carbonic anhydrase enzyme			
A- Dorzolamide	B- Pilocarpine	C-both	D-Atropine
Q10: pilocarpine can be used in treatment of open-angle glaucoma			
A- true	B- false	C-	D-
Q11: NSAIDs are preferable to given preoperatively during cataract surgery for the following reasons:			
A- to induce miosis	B- to induce mydriasis	C-both	D- ..

1	2	3	4	5	6	7	8	9	10	11
B	B	A	A	D	C	A	D	A	A	B

SAQ

Q1) what is the M.O.A and adverse effect of Apraclonidine

Q2)What are the routes of administration on the eye

Q3) Mention 2 Drug classes for treating glaucoma and what is their mechanism of Action?

Q4) You are reviewing a 73-year-old man with multiple cardiac problems. He is currently taking ramipril, metoprolol, furosemide, amiodarone and aspirin. Over the past few months he has noted problems with night glare and his optician has diagnosed corneal microdeposits

a) Which of the drugs was likely the cause of the corneal deposits
b) Enumerate 3 other drugs that can cause corneal deposits

Q5)explain what will happen to the eye if parasympathetic nervous system stimulated

Q6) A 72-year-old man is reviewed in the Emergency Department. He has been feeling tired and unwell for several weeks. There is a past history of glaucoma, chronic obstructive pulmonary disease, congestive heart failure and type-2 diabetes. His GP has recently been investigating for anaemia. Blood tests show a metabolic acidosis with normal anion gap

a) what's the drug most likely to be responsible for the acid base disturbance?
b) Mention its MOA & 2ADRs

Answers

A1) Slide 8

A2) slide 4

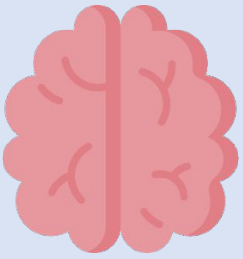
A3) Apraclonidine (↓ production of aqueous humor) ,Acetazolamide (↓Production of aqueous humor by blocking carbonic anhydrase enzyme)

A4) a) Amiodarone. b) Phenothiazines,Sildenafil,Steroids

A5) slide 5

A6) A - Acetazolamide b)↓Production of aqueous humor by blocking carbonic anhydrase enzyme required for production of bicarbonate ions, Myopia, malaise,anorexia GI upset

Feedback Form



Neuropsychiatry Block

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- Rayan Jabaan
- Reem Alqahtani
- Salem Alshihri
- Sara Alharbi
- Sarah Alqahtani
- Shahad Almezel
- Shatha Aldhohair
- Teif Almutiri
- Yara Alasmari