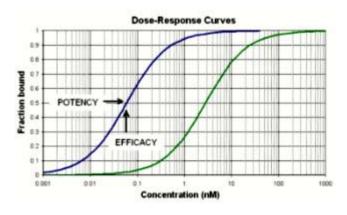
Ocular Pharmacology

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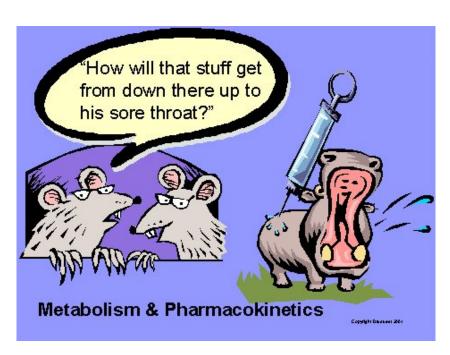
Pharmacodynamics

- 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

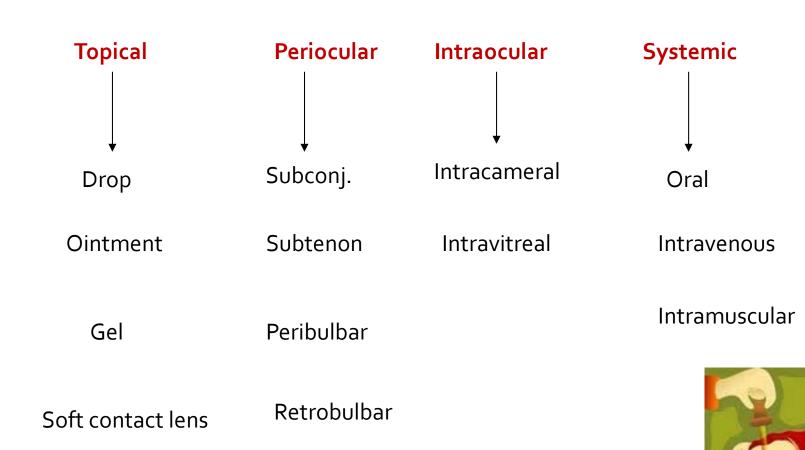


Pharmacokinetics

- Absorption, distribution, metabolism, and excretion of the drug
- A drug can be delivered to ocular tissue as:
 - Locally:
 - Eye drop
 - Ointment
 - Periocular injection
 - Intraocular injection
 - Systemically:
 - Orally
 - IV



Drug Delivery in Eyes



Factors influencing local drug penetration into ocular tissue

- Drug concentration and solubility:: Higher the concentration the better the penetration. e.g pilocarpine 1-4% but limited by reflex tearing
- Viscosity: Addition of methylcellulose and polyvinyl alcohol increases drug penetration by increasing the contact time with the cornea and altering corneal epithelium
- Lipid solubility: because of the lipid rich environment of the epithelial cell membranes, the higher lipid solubility the more the penetration

Amphipathic: Epithelium Lipophilic: Endothelium

Hydrophilic: Stroma

Factors influencing local drug penetration into ocular tissue

- Surfactants:: The preservatives used in ocular preparations <u>alter cell</u> membrane in the cornea 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
- Molecular weight and size

Topical

Drop (Gutta)-

- Simplest and more convenient Mainly for day time use 1 drop=50 microlitre

- Conjuctival sac capacity=7-13 micro liter

So, even 1 drop is more than enough

Method

Hold the skin below the lower eye lid

Pull it forward slightly

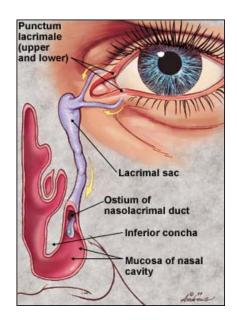
Instill 1 drop





Measures to increase drop absorption:

- -Wait 5-10 minutes between drops -Compress lacrimal sac -Keep lids closed for 5 minutes after instillation
- 50% drug remains 4 min. after instillation
- 10% drug reach aqueous humour
- Compress NLD to decrease systemic absorption





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

- Reach behind iris-lens diaphragm better than topical application
 - Subconjunctival
 - Subtenon, peribulbar,
 - Retrobulbar
- Bypasses 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







Periocular

Subconjunctival: To achieve higher concentration

Drugs which can't penetrate cornea due to large size

Penetrate via sclera

Subtenon: Ant. Subtenon– disease ant to the Lens

Post Subtenon – disease posterior to the lens

Retrobulbar: Optic neuritis

Papillitis

Posterior uveitis

Anesthesia

Peribulbar: Anesthesia



Intraocular injections

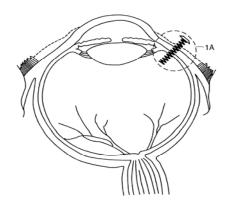
- Intracameral or intravitreal
- E.g.
 - Intracameral acetylcholine (miochol) during cataract surgery
 - Intravitreal antibiotics in cases of endophthalmitis
 - Intravitreal steroid in macular edema
 - Intravitreal Anti-VEGF for DR
 - Distance from limbus for intravitreal injection:
 4 mm phakic, 3.5 mm pseudophakic, 3 mm aphakic



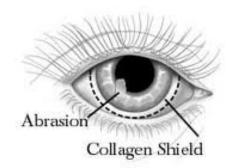


Sustained-release devices

- 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







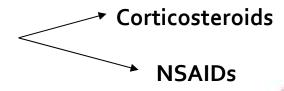
Systemic drugs

- Oral or IV, IM, SC
- Poorly penetrate due to tight junction of retinal vascular endothelium → blood-ocular barrier
- 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



Common ocular drugs

- Antibacterials (antibiotics)
- Antivirals
- Antifungal
- Mydriatics and cycloplegics
- Antiglaucoma
- Anti-inflammatory agents
- Ocular Lubricants
- Antihistaminics
- Ocular diagnostic drugs
- Local anesthetics
- Ocular Toxicology



Antibacterials(Antibiotics)

- Penicillins
- Cephalosporins
- Sulfonamides
- Tetracyclines
- Chloramphenicol
- Aminoglycosides
- Fluoroquinolones
- Vancomycin
- Macrolides

Antibiotics

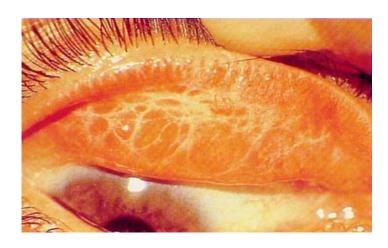
- Used topically in prophylaxis (pre and postoperatively) and treatment of ocular bacterial infections.
- Used orally for the treatment of preseptal cellulitis
 e.g. amoxycillin with clavulonate, cefaclor
- Used intravenously for the treatment of orbital cellulitis
 e.g. gentamicin, cephalosporin, vancomycin, flagyl
- Can be injected intravitrally for the treatment of endophthalmitis





Specific antibiotic for almost each organisms

 Sulfonamiodes- Chlamydial infections like Trachoma Inclusion conjunctivitis Toxoplamosis



Anti-bacterial agent

Cephalosporin

1 st generation

- Cephalothin, cefazolin, cephalexin
- Active against G+ve and G-ve
- Not active against MRSA, Enterobacter, Proteus spp, P aeruginosa, Serratia, enterococci

2 nd generation

- Cefamandole, cefoxitin, cefuroxime
- Greater activity against G-ve : H.influenzae, Enterobacter, Neisseria

3 rd generation

- Cefotaxime, Ceftriaxone, Cefoperazone
- Active against GNR > G+ve cocci : Serratia, Proteus, β-lactamase H influenzae, anaerobe
- P.aeruginosa : ceftazidime, cefoperazone
- Cefotaxime : good penetration blood-ocular barrier

4 th generation

- Extended spectrum
- Against gram-positive organisms as 1 st generation
- Greater resistance to beta-lactamases than 3 rd generation
- Can cross blood brain barrier
- Against nosocomial pathogens
- Cefepime, Cefluprenam, Cefozopran, Cefpirome, Cefquinome



- 1st generation
 - Nalidixic acid
 - Active against G- (not Pseudomonas spp)
- 2nd generation
 - Ciprofloxacin, ofloxacin, lomefloxacin
 - Active against G- including Pseudomonas spp, some G+
 - Not active against Strep pneumoniae
- 3rd generation
 - Levofloxacin
 - Same as 2nd
 - Active against more G+, Strep pneumoniae
- 4th generation
 - Gatifloxacin (Zymar®), moxifloxacin (Vigamox®)
 - Same as 3rd, active against anaerobe
- Useful in bacterial conjunctivitis, corneal ulcer





Amino glycosides

- Mainly against Gm negative bacilli
- Bacterial protein synthesis inhibitors
 - Gentamycin—o.3% eye drop
 - Tobramycin- Pseudomonas 1% eye drop
 - Neomycin—o.3-o.5% eye drop

Tetracycline

- Inhibit protein synthesis
- Active against both gm+ and gm -, some fungi and Chlamydia

Chloromphenicol

- Broad spectrum ,bacteriostatic, gm+/gm-, Chlamydia
- o.5% Eye drop, ointment

- Vancomycin
 - Against MRSA or strep
 - Useful in corneal ulcer, endophthalmitis
- Polymyxin B + Neomycin
 - Against Staph. aureus, Strep spp, GNR
 - Useful in surface bacterial infection e.g. conjunctivitis, blepharitis

Antivirals

Acyclovir

- Ínhibits viral DNA synthesis
- Active against HSV I & II, HZV
- Oral, ointment
- Interact with viral thymidine kinase (selective)
- Used in herpetic keratitis

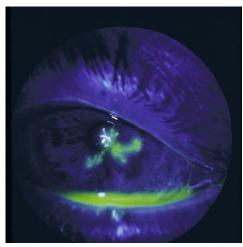
Trifluridine

- Block DNA synthesis, impair RNA replication
- Active against HSV I & II
- More corneal penetration
- Can treat herpetic iritis

Ganciclovir

- Active against CMV
- Oral, iv, intravitreal
- Useful in CMV retinitis
- SE: BM suppression, renal failure
- Used intravenously for CMV retinitis







Antifungals

- Basic fungal classification
- a) Filamentous fungi
 - Septate = Fusarium, Aspergillus
 - Nonseptate = Mucor

b) Yeasts

Candida, Cryptococcus

Most antifungal drugs act by attacking the membrane sterols of fungi (ergosterol), leaving mammalian sterols (cholesterol) unaffected

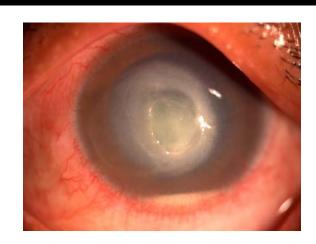
Antifungal

INDICATIONS

Fungal corneal ulcer Fungal retinitis/ Endophthalmitis

Commonly used drugs are

- **Polyenes**
 - Damage cell membrane of susceptible fungi
 - E.g. Amphotericin B, Natamycin, nystatin
 - Side effect: nephrotoxicity
 Imidazoles
- - Increase fungal cell membrane permeability
 - E.g. Miconazole, ketoconazole, fluconazole
 Flucytocine
- - Act by inhibiting DNA synthesis

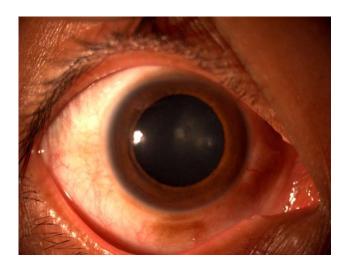


Mydriatics and cycloplegics

- Dilate the pupil, ciliary muscle paralysis
- Classification

Short acting- Tropicamide (4-6 hours)
Intermediate- Homatropine (24 hours)
Long acting- Atropine (2 weeks)

Indications
 Corneal ulcer
 Uveitis
 Cycloplegic refraction



	mydriasis	cycloplegia	duration
atropine	30 min	1 hr	14 days
homatropine	10-30 min	30-90 min	6hr-4 days
scopolamine	40 min	40 min	24 hr
cyclopentolat	e 15-30 min	15-45 min	24 hr
tropicamide	20-30 min	20-25 min	4-6 hr

Cholinergic agonists

Directly acting agonists:

- E.g. pilocarpine, acetylcholine (miochol), carbachol (miostat)
- Uses: miosis, glaucoma
- Mechanisms:
 - 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
- Side effects:
 - Local: diminished vision (<u>myopia</u>), <u>headache</u>, cataract, miotic cysts, and rarely retinal detachment
 - Systemic side effects: lacrimation, salivation, perspiration, bronchial spasm, urinary urgency, nausea, vomiting, and diarrhea



Cholinergic agonists

- Indirectly acting: (anticholinesterases)
 - More potent with longer duration of action
 - Reversible inhibitors
 - E.g. Physostigmine
 - Used in glaucoma and lice infestation of lashes
 - Can cause CNS side effects



Cholinergic agonists

Irreversible:

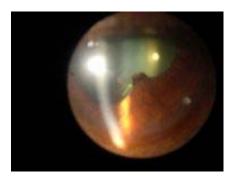
- e.g. Phospholine iodide
- Uses: Accommodative esotropia
- Side effects: Iris cyst and anterior subcapsular cataract
- C/I in angle closure glaucoma, asthma, Parkinsonism
- Causes apnea if used with succinylcholine or procaine



Cholinergic antagonists

- E.g. tropicamide, cyclopentolate, homatropine, scopolamine, atropine
- Cause: mydriasis (by paralyzing the sphincter muscle) with cycloplegia (by paralyzing the ciliary muscle)
- Uses: fundoscopy, cycloplegic refraction, anterior uveitis
- Side effects:
 - 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 delerium

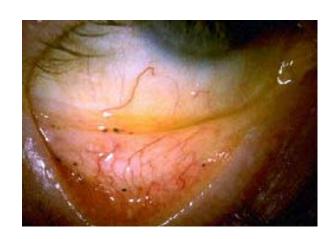






Adrenergic agonists

- Non-selective agonists $(\alpha_1, \alpha_2, \beta_1, \beta_2)$
 - E.g. epinephrine, depevefrin (pro-drug of epinephrine)
 - Uses: glaucoma
 - Side effects: headache, arrhythmia, increased blood pressure, conjunctival adrenochrome, cystoid macular edema in aphakic eyes
 - C/I in closed angle glaucoma



Adrenergic agonists

Alpha-1 agonists

- E.g. phenylephrine
- Uses: mydriasis (without cycloplegia), decongestant
- Adverse effect:
 - 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

Adrenergic agonists

Alpha-2 agonists

- E.g. brimonidine, apraclonidine
- Uses: glaucoma treatment, prophylaxis against IOP spiking after glaucoma laser procedures
- Mechanism: decrease aqueous production, and increase uveoscleral outflow
- Side effects:
 - local: allergic reaction, mydriasis, lid retraction, conjunctival blanching
 - systemic: oral dryness, headache, fatigue, drowsiness, orthostatic hypotension, vasovagal attacks
- Contraindications: Infants, MAO inhibitors users



Alpha adrenergic antagonists

Alpha-1 antagonist

- Inhibits iris dilator by competing with NE for alpha receptors
- E.g. thymoxamine, dapiprazole
- Uses: to reverse pupil dilation produced by phenylepherine
- Not widely used

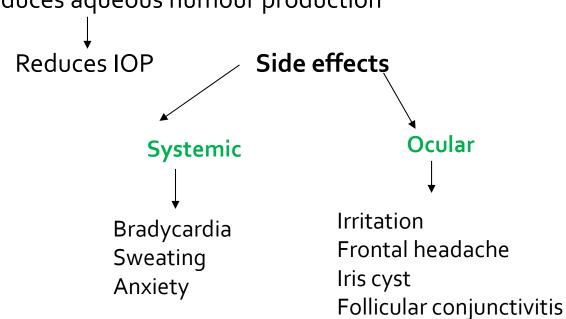
Antiglaucoma drugs

Beta blockers-

- Selective betaxolol
- Non selective- timolol

Mech of action-

Reduces aqueous humour production



Carbonic anhydrase inhibitors

Systemic

Acetazoamide

Topical

Dorzolamide brinzolamide

Mechanism of action: Reduce aqueous humour formation

Side effect

Paresthesiae

Frequent urination

GI disturbances

Hypokalamia

Prostaglandins

- Latanoprost (o.oo5%)
- Bimatoprost (o.o3%)
- Travoprost (o.oo4%)

Mechanism of action: Increased aqueous out flow Side effects: conjunctival congestion, iris and periocular pigmentation, hypertrichosis, darkening of iris

Osmotic agents

- Dehydrate vitreous body which reduce IOP significantly
- E.g.

Glycerine 100% (cause nausea, hyperglycemia)

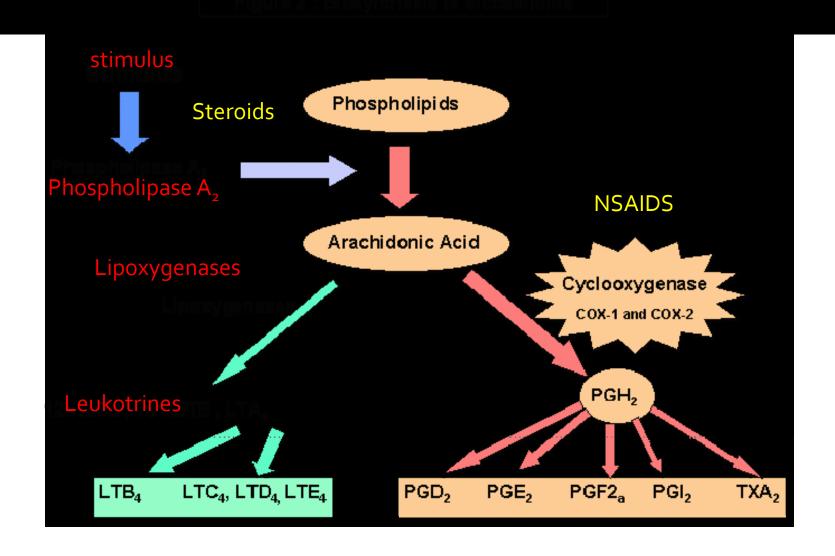
- Dose 1 cc/kg+ juice
- Effect in 30 min. and duration 5-6 hr.

Mannitol 20% IV (cause fluid overload and not used in heart failure)

- Dose 1-2 g/kg IV load in 30 min.
- Effect in 20-60 min. and duration 2-6 hr.



Anti inflammatory drugs



Corticosteroids

Classification

Short acting

Hydrocortisone, cortisone, prednisolone

Intermediate acting

Triamcinolone, Fluprednisolone

Long acting

Dexamethasone, betamethasone

Potency

Cortisone	0.8
-----------------------------	-----

- Hydrocortisone1
- Triamcinolone4
- Prednisolone5
- Dexamethasone 25-30
- Betamethasone 25-30
- Fluorometholone 40-50

Indications for corticosteroids

Topical

Allergic conjunctivitis,

Scleritis,

Uveitis,

allergic keratitis

After intraocular and extra ocular surgeries

Systemic (pathology behind the Lens) Posterior uveitis

Posterior uveitis
Optic neuritis
Corneal graft rejection



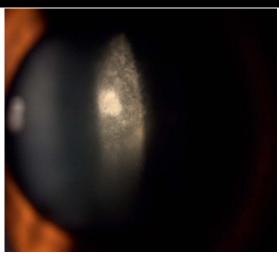
Side effects of corticosteroids

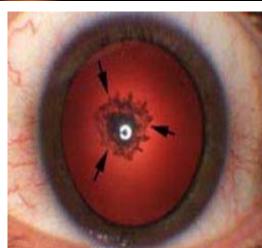
OCULAR

Glaucoma Cataract Activation of infection Delayed wound healing

SYSTEMIC

Peptic ulcer Hypertension Increased blood sugar Osteoporosis Mental changes Activation of tuberculosis and other infections





NSAIDS

Topical use

Flurbiprofen

Indomethacine

Ketorolac

Indications

Episcleritis and scleritis

Uveitis

CME

Pre operatively to maintain dilation of the pupil





Ocular Lubricants

Indication

Ocular irritations in various diseases Dry eyes

Commonly available commercial tear substitutes

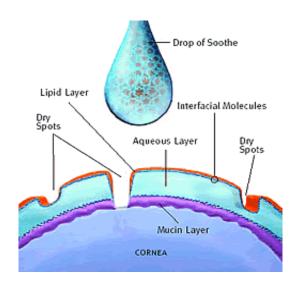
Refresh tears

Tears Naturale II

Tear plus

Moisol

Dudrop



Anti-allergics

- Avoidance of allergens, cold compress, lubrications
- Antihistamines (e.g.pheniramine, levocabastine)
- Decongestants (e.g. naphazoline, phenylepherine, tetrahydrozaline)
- Mast cell stabilizers (e.g. cromolyn, lodoxamide, pemirolast, nedocromil, olopatadine)
- NSAID (e.g. ketorolac)
- Steroids (e.g. fluorometholone, remixolone, prednisolone)
- Drug combinations

Antihistamine

- Pyrilamine maleate, pheniramine maleate, antazoline phosphate
- H1 antihistamine
- Use in allergic conjunctivitis, irritation, pinguecula and pterygium
- Can cause sedation, mydriasis and increase IOP

Vasoconstrictors

Phenylephrine

- Alpha1 agonist
- 0.12-0.125%
- When expose to wind, heat :can cause oxidation
- Can cause mydriasis, blanching of conjunctival vessles, AACG, high BP

Mast-cell stabilizers

- Inhibit histamine and vasoactive substance release from mast-cell
- Use in chronic cases e.g. vernal and seasonal allergic conjunctivitis





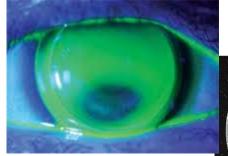


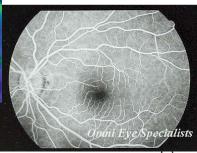
Ocular diagnostic drugs

- 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.









Ocular diagnostic drugs

- 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

Local anesthetics

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

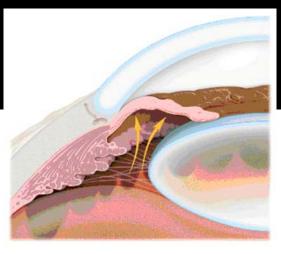


Ocular toxicology

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

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

Digitalis

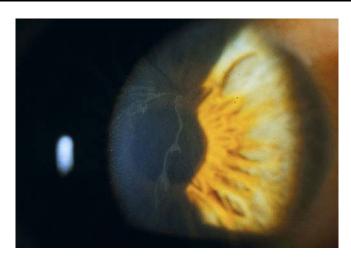
- A cardiac failure drug
- Causes chromatopsia (objects appear yellow) with overdose





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
- Also cause retinopathy (bull's eye maculopathy)



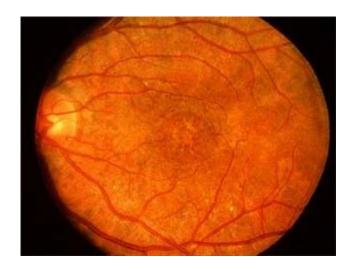


Chorpromazine

- A psychiatric drug
- Causes corneal punctate epithelial opacities, lens surface opacities
- Rarely symptomatic
- Reversible with drug discontinuation

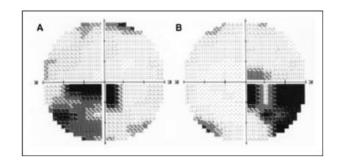
Thioridazine

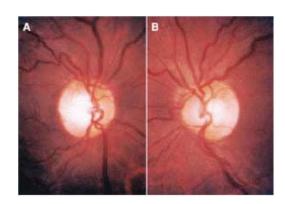
- A psychiatric drug
- Causes a pigmentary retinopathy after high dosage



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)
- Chloramphénicol
- 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)

Other agents

- 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

Thank you for your attention

