Ocular pharmacology and toxicology

Hatem Kalantan, MD
Assistant Professor
Ophthalmology Dept.
College of Medicine
King Saud University
General pharmacological principles
Pharmacodynamics

- It is the biological and therapeutic effect of the drug (mechanism of action)
- Most drugs act by binding to regulatory macromolecules, usually neurotransmitters or hormone receptors or enzymes
- If the drug is working at the receptor level, it can be agonist or antagonist
- If the drug is working at the enzyme level, it can be activator or inhibitor
Pharmacokinetics

- It is the 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
Factors influencing local drug penetration into ocular tissue

- **Drug concentration and solubility:** the higher the concentration the better the penetration e.g. pilocarpine 1-4% but 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
Factors influencing local drug penetration into ocular tissue

- **Surfactants**: the preservatives used in ocular preparations alter cell 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
Eye drops

- Eye drops- most common
- one drop = 50 µl
- volume of conjunctival cul-de-sac 7-10 µl
- measures to increase drop absorption:
  - wait 5-10 minutes between drops
  - compress lacrimal sac
  - keep lids closed for 5 minutes after instillation
Ointments

- Increase the contact time of ocular medication to ocular surface thus better effect
- It has the disadvantage of vision blurring
- The drug has to be high lipid soluble with some water solubility to have the maximum effect as ointment
Peri-ocular injections

- They reach behind iris-lens diaphragm better than topical application
- E.g. subconjunctival, subtenon, peribulbar, or retrobulbar
- This route bypass the conjunctival and corneal epithelium which is good for drugs with low lipid solubility (e.g. penicillins)
- Also steroid and local anesthetics can be applied this way
Intraocular injections

- Intracameral or intravitreal

- E.g.
  - Intracameral acetylcholine (miochol) during cataract surgery
  - Intravitreal antibiotics in cases of endophthalmitis
  - Intravitreal steroid in macular edema
  - Intravitreal Anti-VEGF for DR
Sustained-release devices

- These are devices that deliver an adequate supply of medication at a steady-state level
- E.g.
  - Ocusert delivering pilocarpine
  - Timoptic XE delivering timolol
  - Ganciclovir sustained-release intraocular device
  - Collagen shields
Systemic drugs

- Oral or IV
- Factor influencing systemic drug penetration into ocular tissue:
  - lipid solubility of the drug: more penetration with high lipid solubility
  - Protein binding: more effect with low protein binding
  - Eye inflammation: more penetration with ocular inflammation
Ocular pharmacotherapeutics
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 (myopia), headache, 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 (anti-cholinesterases):
  - 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

- Indirectly acting (anticholinesterases):
  - Irreversible:
    - e.g. phospholine iodide
    - Uses: in 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
  - Treatment by DC or physostigmine
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 increase in blood pressure 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

- E.g. thymoxamine, dapiprazole
- **Uses:** to reverse pupil dilation produced by phenylephrine
- Not widely used
Beta-adrenergic blockers

- E.g.
  - non-selective: timolol, levobunolol, metipranolol, carteolol
  - selective: betaxolol (beta 1 "cardioselective")

- **Uses:** glaucoma

- **Mechanism:** reduce the formation of aqueous humor by the ciliary body

- **Side effects:** bronchospasm (less with betaxolol), cardiac impairment
Carbonic anhydrase inhibitors

- E.g. acetazolamide, methazolamide, dichlorphenamidem, dorzolamide, brinzolamide.
- **Uses:** glaucoma, cystoid macular edema, pseudotumour cerebri
- **Mechanism:** aqueous suppression
- **Side effects:** myopia, parasthesia, anorexia, GI upset, headache, altered taste and smell, Na and K depletion, metabolic acidosis, renal stone, bone marrow suppression “aplastic anemia”
- **Contraindication:** sulpha allergy, digitalis users, pregnancy
Osmotic agents

- Dehydrate vitreous body which reduce IOP significantly

- E.G.
  - glycerol 50% syrup (cause nausea, hyperglycemia)
  - Mannitol 20% IV (cause fluid overload and not used in heart failure)
Prostaglandin analogues

- E.g. latanoprost, bimatoprost, travoprost, unoprostone
- **Uses:** glaucoma
- **Mechanism:** increase uveoscleral aqueous outflow
- **Side effects:** darkening of the iris (heterochromia iridis), lengthening and thickening of eyelashes, intraocular inflammation, macular edema
Anti-inflammatory

corticosteroid

NSAID
Figure 2: Biosynthesis of eicosanoids

Stimulus

Phospholipase A\(_2\) → Phospholipids → Arachidonic Acid

Lipoxygenases:
12-HETE, 15 HETE, LTA\(_4\)

Cyclooxygenase:
COX-1 and COX-2

PGH\(_2\)

PGD\(_2\), PGE\(_2\), PGF\(_2\)\(_a\), PGI\(_2\), TXA\(_2\)

LTB\(_4\), LTC\(_4\), LTD\(_4\), LTE\(_4\)
Corticosteroids

- **Topical**
  - E.g. fluorometholone, remixolone, prednisolone, dexamethasone, hydrocortisone
  - **Mechanism:** inhibition of arachidonic acid release from phospholipids by inhibiting phospholipase A2
  - **Uses:** postoperatively, anterior uveitis, severe allergic conjunctivitis, vernal keratoconjunctivitis, prevention and suppression of corneal graft rejection, episcleritis, scleritis
  - **Side effects:** susceptibility to infections, glaucoma, cataract, ptosis, mydriasis, scleral melting, skin atrophy
Corticosteroids

- **Systemic:**
  - E.g. prednisolone, cortisone
  - **Uses:** posterior uveitis, optic neuritis, temporal arteritis with anterior ischemic optic neuropathy
  - **Side effects:**
    - Local: *posterior subcapsular cataract*, glaucoma, central serous retinopathy
    - Systemic: suppression of pituitary-adrenal axis, hyperglycemia, osteoporosis, peptic ulcer, psychosis
NSAID

- E.g. ketorolac, diclofenac, flurbiprofen
- **Mechanism:** inactivation of cyclooxygenase
- **Uses:** postoperatively, mild allergic conjunctivitis, episcleritis, mild uveitis, cystoid macular edema, preoperatively to prevent miosis during surgery
- **Side effects:** stinging
Anti-allergics

- Avoidance of allergens, cold compress, lubrications
- **Antihistamines** (e.g. pheniramine, levocabastine)
- **Decongestants** (e.g. naphazoline, phenylepherine, tetrahydrozoline)
- **Mast cell stabilizers** (e.g. cromolyn, lodoxamide, pemirolast, nedocromil, olopatadine)
- **NSAID** (e.g. ketorolac)
- **Steroids** (e.g. fluorometholone, mixolone, prednisolone)
- Drug combinations
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. amoxicillin with clavulonate, cefaclor
- Used **intravenously** for the treatment of orbital cellulitis e.g. gentamicin, cephalosporin, vancomycin, flagyl
- Can be injected **intravitreally** for the treatment of endophthalmitis
Antibiotics

- **Trachoma** can be treated by topical and systemic tetracycline or erythromycin, or systemic azithromycin.
- **Bacterial keratitis** (bacterial corneal ulcers) can be treated by topical fortified penicillins, cephalosporins, aminoglycosides, vancomycin, or fluoroquinolones.
- **Bacterial conjunctivitis** is usually self limited but topical erythromycin, aminoglycosides, fluoroquinolones, or chloramphenicol can be used.
Antifungals

- **Uses:** fungal keratitis, fungal endophthalmitis
- **Polyenes**
  - damage cell membrane of susceptible fungi
  - e.g. amphotericin B, natamycin
  - side effect: nephrotoxicity
- **Imidazoles**
  - increase fungal cell membrane permeability
  - e.g. miconazole, ketoconazole
- **Flucytocine**
  - act by inhibiting DNA synthesis
Antivirals

- **Acyclovir**
  - Interact with viral thymidine kinase (selective)
  - Used in herpetic keratitis

- **Trifluridine**
  - More corneal penetration
  - Can treat herpetic iritis

- **Ganciclovir**
  - Used intravenously for CMV retinitis
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, goniscopy, 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
Other ocular preparations

- **Lubricants**
  - drops or ointments
  - Polyvinyl alcohol, cellulose, methylcellulose
  - Preserved or preservative free
Ocular toxicology
Complications of topical administration

- **Mechanical injury** from the bottle e.g. corneal abrasion
- **Pigmentation:** epinephrine-adrenochrome
- **Ocular damage:** e.g. topical anesthetics, benzylkonion
- **Hypersensitivity:** e.g. atropine, neomycin, gentamicin
- **Systemic effect:** topical phenylephrine can increase BP
Amiodarone

- A cardiac arrhythmia drug
- Causes **optic neuropathy** (mild decreased vision, visual field defects, bilateral optic disc swelling)
- Also causes corneal vortex keratopathy (corneal verticillata) which is whorl-shaped pigmented deposits in the corneal epithelium
Digitalis

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

- E.g. chloroquine, hydroxychloroquine
- Used in malaria, rheumatoid arthritis, SLE
- Cause vortex keratopathy (corneal verticillata) which is usually asymptomatic but can present with glare and photophobia
- 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
Diphenylhydantoin

- An epilepsy drug
- Causes dosage-related cerebellar-vestibular effects:
  - Horizontal *nystagmus* in lateral gaze
  - *Diplopia*, *ophthalmoplegia*
  - *Vertigo*, *ataxia*
- Reversible with the discontinuation of the drug
Topiramamate

- A drug for epilepsy
- Causes acute angle-closure glaucoma (acute eye pain, redness, blurred vision, haloes).
- Treatment of this type of acute angle-closure glaucoma is by cycloplegia and topical steroids (rather than iridectomy) with the discontinuation of the drug
Ethambutol

- An anti-TB drug
- Causes a dose-related optic neuropathy
- Usually reversible but occasionally permanent visual damage might occur
Agents that Can Cause Toxic Optic Neuropathy

- Methanol
- Ethylene glycol (antifreeze)
- Chloramphenicol
- Isoniazid
- Ethambutol
- Digitalis
- Chloroquine
- Streptomycin
- Amiodarone
- Quinine
- Vincristine and methotrexate (chemotherapy medicines)
- Sulfonamides
- Melatonin with Zoloft (sertraline, Pfizer) in a high-protein diet

- Carbon monoxide
- Lead
- Mercury
- Thallium (alopecia, skin rash, severe vision loss)
- Malnutrition with vitamin B-1 deficiency
- Pernicious anemia (vitamin B-12 malabsorption phenomenon)
- Radiation (unshielded exposure to >3,000 rads).
HMG-CoA reductase inhibitors (statins)

- Cholesterol lowering agents
- E.g. pravastatin, lovastatin, simvastatin, fluvastatin, atorvastatin, rosuvastatin
- Can cause cataract in high dosages specially if used with erythromycin
Other agents

- **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

Any question?