Ocular Pharmacology

Dr Parul Ichhpujani
Assistant Professor
Deptt. Of Ophthalmology,
Government Medical College and Hospital, Sector 32, Chandigarh
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

Topical
- Drop
- Ointment
- Gel
- Soft contact lens

Periocular
- Subconj.
- Subtenon
- Peribulbar
- Retrobulbar

Intraocular
- Intracameral
- Intravitreal

Systemic
- Oral
- Intravenous
- Intramuscular
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 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.

- **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 vision blurring
- 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
**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

- Corticosteroids
- NSAIDs
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 **intravitreally** for the treatment of endophthalmitis
Specific antibiotic for almost each organisms

- **Sulfonamides** - Chlamydial infections like Trachoma
  - Inclusion conjunctivitis
  - Toxoplasmosis
Cephalosporin

1st generation
- Cephalothin, cefazolin, cephalexin
- Active against G+ve and G-ve
- Not active against MRSA, Enterobacter, Proteus spp, P aeruginosa, Serratia, enterococci

2nd generation
- Cefamandole, cefoxitin, cefuroxime
- Greater activity against G-ve : H.influenzae, Enterobacter, Neisseria

3rd 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
4th generation
- Extended spectrum
- Against gram-positive organisms as 1st generation
- Greater resistance to beta-lactamases than 3rd generation
- Can cross blood brain barrier
- Against nosocomial pathogens
- Cefepime, Cefluprenam, Cefozopran, Cefpirome, Cefquinome
### Fluoroquinolones

- **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—0.3% eye drop
  - Tobramycin—Pseudomonas 1% eye drop
  - Neomycin—0.3-0.5% eye drop
**Tetracycline**
- Inhibit protein synthesis
- Active against both gm+ and gm-, some fungi and Chlamydia

**Chloromphenicol**
- Broad spectrum, bacteriostatic, gm+/gm-, Chlamydia
- 0.5% 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**
  - Inhibits 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
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

- **Flucytosine**
  - 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
<table>
<thead>
<tr>
<th>Drug</th>
<th>Mydriasis</th>
<th>Cycloplegia</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atropine</td>
<td>30 min</td>
<td>1 hr</td>
<td>14 days</td>
</tr>
<tr>
<td>Homatropine</td>
<td>10-30 min</td>
<td>30-90 min</td>
<td>6 hr-4 days</td>
</tr>
<tr>
<td>Scopolamine</td>
<td>40 min</td>
<td>40 min</td>
<td>24 hr</td>
</tr>
<tr>
<td>Cyclopentolate</td>
<td>15-30 min</td>
<td>15-45 min</td>
<td>24 hr</td>
</tr>
<tr>
<td>Tropicamide</td>
<td>20-30 min</td>
<td>20-25 min</td>
<td>4-6 hr</td>
</tr>
</tbody>
</table>
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: (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
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
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 phenylephrine
- Not widely used
Antiglaucoma drugs

- Beta blockers-
  - Selective – betaxolol
  - Non selective - timolol

Mech of action-
Reduces aqueous humour production

Reduces IOP

Side effects

- Systemic
  - Bradycardia
  - Sweating
  - Anxiety

- Ocular
  - Irritation
  - Frontal headache
  - Iris cyst
  - Follicular conjunctivitis
Carbonic anhydrase inhibitors

Systemic
Acetazolamide

Topical
Dorzolamide
brinzolamide

Mechanism of action: Reduce aqueous humour formation

Side effect
Paresthesiae
Frequent urination
GI disturbances
Hypokalamia
Prostaglandins

- Latanoprost (0.005%)
- Bimatoprost (0.03%)
- Travoprost (0.004%)

**Mechanism of action:** Increased aqueous outflow

**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

Figure 2: Biosynthesis of eicosanoids

- Stimulus
- Steroids
- Phospholipase A₂
- Lipoxygenases
- Leukotrienes
  - LTB₄, LTC₄, LTD₄, LTE₄

Phospholipids → Arachidonic Acid → Cyclooxygenase (COX-1 and COX-2) → PGH₂ → PGD₂, PGE₂, PGF₂α, PGI₂, TXA₂

NSAIDS
Corticosteroids

Classification

Short acting
   Hydrocortisone, cortisone, prednisolone

Intermediate acting
   Triamcinolone, Fluprednisolone

Long acting
   Dexamethasone, Betamethasone
- **Potency**
  - Cortisone 0.8
  - Hydrocortisone 1
  - Triamcinolone 4
  - Prednisolone 5
  - 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
- Optic neuritis
- Corneal graft rejection

NEVER GIVE STEROID IF YOU ARE SUSPECTING ACTIVE INFECTION
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 vessels, 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
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
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)

- 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