Ocular pharmacology

Section 1
Pharmacologic principles
Especial forms and administrations
routes of eye drugs

Section 2
Ocular pharmacotherapeutics
Current and common drug groups
Pharmacokinetics

To achieve a therapeutic effect, a drug must reach its site of action in sufficient concentration:

- Amount administered
- Extent & rate of absorption at the administration site
- Distribution & binding in tissues
- Movement by bulk flow in circulating fluids
- Transport between compartments
- Biotransformation
- Excretion
Eye drops

- Most ocular medications
- Adequate concentration in anterior segment
- Without incurring unwanted effects in other systems
Eye drops

Some features limit its effectiveness:
* Very little of an administered drop

When a 50 μl eye drop is delivered, the volume of lachrymal fluid rises about 10 μl in the blinking eye of an upright patient. (20% of administered drug is retained)
* Rapid turnover of fluid, 16% per minute, and much more if the drop elicits reflex tearing
Eye drop

Some measures improve ocular absorption:

- More than one eye drop → wait 5 minutes between drops
- Compress the nasolachrymal duct to prevent egress of tears and to reduce systemic absorption through the nasal mucosa
Eye drop

- Contact time of eye drop medication is short,
- The rate of transfer from the tear fluid into the cornea is critical.
- Corneal epithelium and endothelium have tight intercellular junctions
- Drug concentration
- Solubility
- Viscosity
- Reflex tearing
Solubility

To traverse the cornea, a drug must pass in turn through:

- Lipid rich environment of the epithelial cell membrane
- Water rich environment of the stroma
- Lipid barrier at the endothelium
Reflex tearing

- Reduces the contact time of the drug with the cornea
- Any physical contact that elicit blinking reflex
- PH value very different from 7.4
Ointments

- Increasing the contact time of ocular medications
- Consist of petrolatum and mineral oil
- Melt at body temperature
Periocular injections

- Sub conjunctiva
- Sub tenon
- Retrobulbar
- Peribulbar
Intraocular injections

- Intracameral
- Intravitreal
Systemic therapy

- Blood ocular barriers limit access through vascular channels
- More readily penetrated by drugs with higher lipid solubilities
- The unbound to plasma proteins drugs can cross the blood ocular barriers
Cholinergic agents

- Affect the activity acetylcholine receptors in synaps of the peripheral nervous system
- parasympathetic effectors sites are in the iris sphincter and ciliary body
Cholinergic agents

- Direct acting agonists act on the receptor to elicit an excitatory postsynaptic potential.
- Indirect acting agonists inhibit the acetylcholine esterase of the synaptic cleft, preventing deactivation of endogenous acetylcholine.
- Antagonists block the action of acetylcholine on the receptors.
Cholinergic agents

- Parasympathomimetic agents:
  - Contraction of the iris sphincter (miosis) and changes the anatomical relationship of the iris to the lens and chamber angle
  - Contraction of the circular fibers of the ciliary muscle (accommodation)
  - Contraction of the longitudinal fibers of the ciliary muscle (outflow facility↑)
Parasympathomimetic agents

- Miosis $\rightarrow$ narrow angle glaucoma
- Accommodation $\rightarrow$ accommodative esotropia
- Increasing outflow facility $\rightarrow$ open angle glaucoma
accommodative esotropia

- The near response is a synkinetic of accommodation, miosis and convergence.
- Parasympathomimetic agents reduce the need to accommodate, the patient not only experience less accommodation but also less convergence.
Parasympathomimetic agents

- Acetylcholine (miochol) → intracameral
- Carbacol (more effective and longer lasting) → intracameral
- Pilocarpine 0.12% confirm Adie tonic pupil
  " 1-6% in the treatment of glaucoma
Parasympathomimetic agents

**Side effects:**

- Miosis
- Induced myopia and accommodation
- Cataractogenesis
- Retinal tear or even rhegmatogenous detachment
Parasympathomimetic agents

Indirect agonist such as echothiophate (phospholine iodide)

- Longer duration of action
- Frequently more potent
- Twice daily treatment is sufficient
Parasympathomimetic antagonist

- Paralysis of the iris sphincter → mydriasis → facilitating fundus examination, preventing posterior synechia
- Paralyze the ciliary muscle → inhibit accommodation, relieve pain associated with iridocyclitis, accurate refraction
<table>
<thead>
<tr>
<th>Parasympathomimetic antagonist</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atropine</td>
</tr>
<tr>
<td>Homatropine</td>
</tr>
<tr>
<td>Cyclopentolate</td>
</tr>
<tr>
<td>Tropicamide</td>
</tr>
</tbody>
</table>
Parasympathomimetic antagonist

Side effects:
- Ocular → due to midriasis
- Systemic → dose related toxicity

Flash, fever, tachycardia, ……
Adrenergic receptors

- $\alpha_1$ mediate smooth muscle contraction
- $\alpha_2$ mediate feedback inhibition of presynaptic sympathetic
- $\beta_1$ predominantly in the heart
- $\beta_2$ mediate relaxation of smooth muscle in most blood vessels and in the bronchi
**α₁** adrenergic agonist

- Stimulation of the iris dilator muscle \( \Rightarrow \) mydriasis
- Systemic absorption may elevate systemic blood pressure
- Such as phenylephrine
$\alpha_2$ adrenergic agonist

- Prevents release of norepinephrine at nerve terminals
- Decrease aqueous production as well as episcleral venous pressure & improves trabecular outflow
- Such as apraclonidine hydrochloride
$\alpha_1$ adrenergic antagonist

- Inhibit adrenergic tone to the dilator muscle $\Rightarrow$ miosis
- Differentiating angle closure glaucoma from POAG
- Such as thymoxamine
**β₂ adrenergic agonist**

- Lower IOP by increasing uveoscleral outflow and perhaps through the trabecular meshwork
- L-epinephrine (α, β agonist)
- Side effects: black deposits in the conjunctiva
  - Reversible cystoid maculopathy (25% of aphakic eyes)
β adrenergic antagonist

β blocker

- Lower IOP by reducing aqueous humor production as much as 50%
- Timolol maleate (timoptic) and levobunolol (betagan) are mixed β₁, β₂ antagonists
$\beta_1$ adrenergic antagonist

- Significantly safer when pulmonary, cardiac, CNS or other systemic conditions are considered
- Such as Betaxolol (a selective drug)
Carbonic anhydrase inhibitor

- Mechanisms of aqueous secretion are not fully understood
- Decrease of aqueous secretion depend on active transport of Na by Na\(^+\), K\(^+\), ATPase on the surface of nonpigmented epithelial cells
- Na\(^+\) transport partially linked to HCO\(_3^-\) formation
- HCO\(_3^-\) formation reduced by inhibition of the enzyme carbonic anhydrase
CAIs drugs

- **Systemic**: Acetazolamide (diamox) 250-500mg, 4-6h duration of action
  - Methazolamide
- **Topical**: Dorzolamide (trusopt)
  - Brinzolamide (azopt)

Treatment of all glaucomas
CAIs drugs side effects

- Metabolic acidosis
- Urinary tract stone formation
- Numbness and tingling of the hands, feet and lips
- Malaise
- Anorexia and weight loss, nausea
- Depression
Prostaglandin analogs

- New class of ocular hypertensive agents
- Latanoprost (Xalatan)
  Lower IOP by enhancing uveoscleral outflow
  - reduce the pressure (25-35%)

Once daily dosing
Lack of cardiopulmonary effects
Ocular side effects: darkening of the iris and periocular skin, cystoid macular edema, uveitis
Osmotic agents

- Reduce IOP and vitreous volume by drawing fluid out of the eye across vascular barriers
- Used in the short management of acute glaucoma and prior to cataract surgery
- Used with care in cardiovascular disorders: CHF, hypertension, recent MI
### Hyperosmotic Agents

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Trade Name</th>
<th>Preparation</th>
<th>Dose</th>
<th>Route</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glycerin</td>
<td>Osmoglyn</td>
<td>50%</td>
<td>1–1.5 g/kg</td>
<td>Oral</td>
</tr>
<tr>
<td>Isosorbide</td>
<td>Ismotic</td>
<td>45%</td>
<td>1.5 g/kg</td>
<td>Oral</td>
</tr>
<tr>
<td>Mannitol</td>
<td>Osmitrol</td>
<td>5%–20%</td>
<td>0.5–2 g/kg</td>
<td>IV</td>
</tr>
<tr>
<td>Urca</td>
<td>Ureaphil</td>
<td>Powder or 30% soln</td>
<td>0.5–2 g/kg</td>
<td>IV</td>
</tr>
</tbody>
</table>
Anti inflammatory agents

- glucocorticoids
- Non Steroidal Anti-Inflammatory Agents (NSAIDs)
- Antihistamine
- Histamine release blocker
- Anti fibrotics
Glucocorticoids

- Prevent or suppress corneal graft rejection

<table>
<thead>
<tr>
<th>Anterior chamber reaction</th>
<th>Immune or traumatic</th>
</tr>
</thead>
<tbody>
<tr>
<td>uveitis</td>
<td>Severe ocular inflammation:</td>
</tr>
<tr>
<td>Subconj, retrobulbar, systemic</td>
<td>Glucocorticoids</td>
</tr>
</tbody>
</table>
Adverse effects of glucocorticoids

- Glaucoma
- Post subcapsualr cataract
- Exacerbation of bacterial and viral infection
- Ptosis, mydriasis, scleral melting
- Suppression of the pituitary adrenal axis
- Gluconeogenesis
- Peptic ulcer
<table>
<thead>
<tr>
<th>CONDITION</th>
<th>ROUTE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blepharitis</td>
<td>Topical</td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>Topical</td>
</tr>
<tr>
<td>Episcleritis</td>
<td>Topical</td>
</tr>
<tr>
<td>Scleritis</td>
<td>Topical and/or systemic</td>
</tr>
<tr>
<td>Keratitis</td>
<td>Topical</td>
</tr>
<tr>
<td>Anterior uveitis</td>
<td>Topical and/or periocular</td>
</tr>
<tr>
<td>Posterior uveitis</td>
<td>Systemic and/or periocular, intravitreal</td>
</tr>
<tr>
<td>Endophthalmitis</td>
<td>Systemic/periocular, intravitreal</td>
</tr>
<tr>
<td>Optic neuritis</td>
<td>Systemic or periocular</td>
</tr>
<tr>
<td>Cranial arteritis</td>
<td>Systemic</td>
</tr>
<tr>
<td>Sympathetic ophthalmia</td>
<td>Systemic and topical</td>
</tr>
</tbody>
</table>
NSAIDs

- Salicylates: aspirin, mefenamic acid
- Indoles: indomethacin
- Phenyl alkanoic acid: diclofenac, ibuprofen, naproxen
- Pyrazolones: phenylbutazone
Mast cell stabilizer & antihistamine

- Allergic conjunctivitis: an immediate hypersensitivity reaction (IgE)
- Released histamine: capillary dilation & increased permeability → injection & swelling
- Topical antihistamine: antazoline → mild allergic symptoms
Cromolyn sodium

- Blocker of histamine release
- The therapy of choice for severe vernal & atopic conjunctivitis
Anti proliferative agents

- In the treatment of severe ocular inflammatory diseases:
  - Behjet syndrome
  - Sympathetic ophthalmia

- Fluorouracil – mitomycin C
Antibiotic therapy

- Drug penetration in cornea
- Blood ocular barriers
- Select effective antibiotics
- Gram stain, culture and antibiogram
- Immediate intravitreal injection of broad spectrum antibiotics in severe endophthalmitis
Antibacterial agents

- Penicillin's
- Cephalosporine
- Sulfonamids
- Tetracycllin
- Chloramphenicol
- Aminoglycosids
- Fluoroquinolones
Antifungal

- Polyenes: natamycin 5% suspension for topical ophthalmic use
- Amphotericin B at 0.25% - 0.5% in sterile water
- These agents penetrate the cornea poorly
- Active topically against a variety of filamentous fungi: aspergillus, cephalosporium, fusarium, penicillium, yeast candida albicans
Antifungal

- **Imidazols:** miconazole 1% solution subconjunctivally or topically
- Miconazole penetrate the cornea poorly
- **Ketoconazole 200 mg tablet** (every 6-8h)
- Penetrates the blood – ocular barrier poorly but therapeutic levels can be achieved in inflamed eyes
- **Aspergillus, coccidioides, cryptococcus**, & candida
Antifungal

- Flucytosine: orally at 50 - 150 mg/kg daily divided into four doses
- Penetrates the blood ocular barrier well
- Use primarily as an adjunct to systemic amphotericin B therapy
Antiviral agents

- Topical:
  - idoxuridine
  - trifluridine (TFT)
  - vidarabine
Antiviral agents

- **Systemic:**
  - Acyclovir → herpes zoster, prevent of HSV keratitis
  
Can be used topically, orally or intravenously
Medication for acanthamoeba infection

- A corneal pathogen → contact lens users
- No single drug is effective in treating all acanthamoeba keratitis
- Polyhexamethylene biguanid (0.02% solution) first line agent
- Chlorhexidine, neomycin, polymyxin, B gramicidin, mixtures, natamycine 5%
Anesthetics agents

- Local: retrobubar and eyelid blocks → excellent anesthesia for surgery.
Anesthetics agents

- Esters: proparacaine, tetracaine
- Amides: lidocaine 40–60 min, bupivacain (marcaine) long acting several hours