

BASIC OCULAR PHARMACOLOGY
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1. Routes of ocular drug delivery

a. Drops

- Easy drug delivery to eye with limited systemic absorption
- Better compliance with less frequency of drops

b. Ointments

- Increase contact time of drug with eye.
- Consist of petrolatum and mineral oil base.
- Drugs with high lipid and some water solubility can achieve high aqueous levels
- May impede absorption of other drugs by forming a barrier
- Distort vision.
- Often used for lubrication purposes.
- Sustained release formulations possible (Timoptic XE).
- Examples: Erythromycin, polytrim, Ciloxan, Pilogel, Muro.

c. Subtenons Injection

- Allow drugs to bypass the conjunctival and corneal epithelial barriers.
- Can allow drugs to reach higher intraocular levels behind the lens-Iris diaphragm.

d. Intra-Ocular Injection

- Instant delivery of high concentration at target site.
- Therapeutic levels can be very narrow before toxicity.
- In the past primarily used to treat endophthalmitis.
- Upcoming indications include diabetic macular edema and macular degeneration.
- Can be done in office / procedure room
- Example: Lucentis, Avastin, Kenalog & Triescence

e. Systemic (Oral/IV)

- Like the blood-brain barrier, the blood-eye barrier is quite strong.
- It is made by tight intercellular junctions surrounding vessels.
 - i. Although choroid and ciliary body have fenestrated vascular endothelium, they are surrounded by epithelium with tight junctions.
 - ii. The barrier is better penetrated by highly lipid soluble drugs
- Only drug not bound to plasma proteins can cross the BRB.
- Bolus administration of drug overwhelms protein binding for better penetration.
- BRB crossed better when eye is inflamed. e.g. Fluorescein in vitreous after angiogram in inflamed eye.
- Sustained release drugs such as Diamox sequels also useful but slow acting in acute situations.
- IV Mannitol and Diamox useful drugs to lower pressure in OR.

2. Factors Influencing ocular drug bioavailability

a. Concentration and solubility

- The higher the concentration, the larger amount of drug potentially available.
- Too high a concentration can exceed the solubility of the drug or can increase tonicity of tears and thus induce reflex tearing that can wash the drug out.
- First order kinetics: drug transfer rate proportional to concentration.
- Zero order kinetics: drug transfer rate independent of concentration and determined by the body's capacity to transfer.

b. Contact time

- The longer the drug can be kept in contact with the corneal surface, the higher the absorption.
- Improved by punctal occlusion, eye closure and waiting 5 min between drops.

c. Lipid solubility

- In order to reach the anterior chamber, the drug has to cross the lipid rich corneal epithelial membranes, the water rich stroma and lipid rich endothelial surface.
- Experiments show that the lipid solubility is more critical.
- Altering the PH of solution changes the lipophilic or hydrophilic component of the drugs. But, changing the pH from 7.4 too much may induce reflex tearing.

d. Surfactants

- Some compounds such as benzylkonium alter cell membranes in bacteria and the cornea and can increase drug penetration as much as 20 fold.

e. Distribution, Breakdown & Excretion

3. Commonly used ocular drugs

a. Mydriatic Agents

- Iris dilator innervated by sympathetic adrenergic fibers
 - Phenylephrine: Alpha 1 direct acting agonist: dilates eye for 3-5 hrs.
 - Parasympathetically innervated Iris sphincter much stronger, thus incomplete dilation with phenylephrine alone- need a cycloplegic agent also.
 - Side effects: worsens hypertension, vasoconstriction, increased peripheral resistance, increased closure of internal sphincter of bladder.

b. Cycloplegic + Mydriatic Agents

- Iris sphincter & ciliary muscle innervated by parasympathetic muscarinic fibers. Agents that block the cholinergic stimulation at these sites induce dilation and cycloplegia (paralysis of accommodation).
 - Atropine (7-14 days), Scopolamine (3-7 days), Homatropine (1-3 days), Cyclopentolate (1 day), Tropicamide (6 hrs).
 - Used in preop mydriasis and in uveitis for comfort.
 - Avoid in narrow angle glaucoma until Iridotomy done.
 - Side Effects: blurred vision, hyperemia, psychotic reaction and behavioral disturbances in children, seizures, coma, angle closure.

c. Miotic Agents

- Direct Acting Agents: Increase cholinergic stimulation of parasympathetic muscarinic receptors on iris sphincter and ciliary muscle.

- Useful in narrow angle glaucoma until iridectomy done. Used more often in past for open angle glaucoma to increase aqueous outflow.
- Can induce myopia and cause difficulty in people with cataracts.
- Example: Miochol- used intraoperatively to induce miosis after placement of IOL, during PK and Iridectomy; Pilocarpine drops.
- Risk of retinal detachment by stretching force generated by miosis, supraorbital headache, ciliary spasm.
- Indirect Acting Agents: work by blocking the cholinesterase enzyme that breaks down acetylcholine and allow prolonged acetylcholine activity.
 - Phospholine Iodide: Used in open angle glaucoma in past, and can be used for accommodative esotropia in children.
 1. Avoid in inflamed eye, may cause iris cysts in children and cataracts in adults. Muscle relaxants during general anesthesia can cause prolonged paralysis. Avoid insecticide exposure when using these drugs.

d. Anti-Inflammatory

- Steroids
 - Dexamethasone 0.1%
 - Prednisolone Acetate 0.12% to 1%.
 - Flouromethalone 0.1% to 0.25%
- Nonsteroid Anti-Inflammatory Drugs
 - Voltaren, Ocufer, Acular, Xibrom, Nevnac
- Antihistamines and Cromolyn Sodium
 - Cromolyn Sodium 4%, Alomide, Patanol, Pataday

e. Antibiotics

- Topical: Vigamox, Zymar, etc
- Injected: Gentamicin, Ancef, Vancomycin, Ceftazidime, etc.

f. Intraocular Pressure Lowering Agents

- Beta Blockers
- Alpha2 Agonist: Alphagan P replacing Alphagan
- Prostaglandin Analogs & Prostanoids: Xalatan, Lumigan, Travatan, Rescula.
- Carbonic Anhydrase Inhibitors
 - Trusopt, Azopt
 - Diamox, Neptazane
- Osmotic Agents
 - Osmoglyn (Glycerin 50%) Use orally at 1-1.5 g/kg
 - Isosorbide 45%: Use orally at 1.5 g / kg
 - Mannitol 5%-20%. Use IV 0.5-2g/ kg

g. Anti-VEGF

- Avastin, Lucentis

Ref: Adapted from AAO Basic & Clinical Science Course Sect. 2 and 2001 ASORN basic pharmacology presentation.