OCULAR PHARMACOLOGY I

Part One: General Pharmacology Principles; Drug Delivery Systems; Topical Anesthetics; Viscoelastics; Dilating Solutions for Cataract Surgery

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PHARMACOTHERAPEUTICS

- Administration of drug to reach a given clinical endpoint: treatment or prevention of disease
- Therapeutic dose depends on patient age, sex, race, other meds taken and other medical conditions
Ocular Pharmacology

- **Pharmacokinetics:**
  - Substances cycling through biological tissue
  - Absorption
  - Distribution
  - Metabolism
  - Excretion
  - With the dose of the med these determine the bioavailability at the site of intended action

- **Pharmacodynamics:**
  - Biological and chemical effects of chemical on the biological system
  - Tissue receptor for the drug
  - Intracellular changes initiated by the drug
  - Categorized by the receptor for the drug i.e. alpha agonist
TOXICITY

- Eye drops avoid first pass metabolism by the liver and increases systemic bioavailability
- Systemic toxicity may be more than expected from topical dose
- Neonates, infants have less developed drug metabolism and excretion
- Local toxicity is more common than systemic toxicity with type I (IgE) mediated hypersensitivity or delayed reaction type 4
TOXICITY

- **Preservatives** can be toxic to ocular surface can enhance corneal permeability. Common preservatives in ophthalmic preparations:
  - Benzalkonium chloride (BAK)
  - Thimerosal
  - Chlorobutanol
  - Parahydroxybenzoates
  - Aromatic alcohols
NEWER PRESERVATIVES REDUCE TOXICITY

- **Disappearing preservatives** theoretically should have no toxicity to the corneal surface
- Preservative dissipates with exposure to light or to ions in the tear film
- Disappearing preservatives: **oxychloro complex** breaks down into sodium chloride and water. **Sodium perborate** breaks down to hydrogen peroxide then to hydrogen and water
NEWER PRESERVATIVES

- Ionic buffer with borate, sorbitol, propylene glycol and zinc breaks down on exposure to tear film cations
- Poly quad (polyquaternium-1): detergent that is repelled by corneal epithelium
- Preservative-free single-use preparations are also an alternative
PHARMACOKINETICS: CORNEAL TRANSFER: TIGHT JUNCTIONS EPITHELIUM/ENDOTHELium

- Need to be lipophilic and hydrophobic epithelium and endothelium; stroma is hydrophilic and lipophobic
- Meds must be lipophilic and hydrophilic
- Lipid solubility to water solubility ratio
- Non-ionic pass through cell membranes more readily
- pH of medication can be changed to increase the percentage in a non-ionic form of the medication to increase absorption
- Solutions vs suspensions: solubility in the tear film meds with poor water solubility are formulated as suspensions
- Viscosity increases the retention of the such as Timolol GFS
- Limits to the amount of viscosity: sticky sensation may result and may cause surface irritation
ELDERLY PATIENTS

- Less lean body mass
- Less body water and albumin
- Higher relative percentage of adipose tissue
- Results in alterations in tissue binding and drug distribution
- Take multiple meds that can affect metabolism
- Hepatic and renal systems also decrease with age

- Extends the half life of most mediations in the elderly
- The action of the drug is potentiated
- Therapeutic and toxic effects of a medication may be altered by the aging process independent of the drug dosage
Topical, Systemic, Periocular, Intracameral, Intravitreal
CORNEAL PENETRATION BY DRUGS

- Concentration of the medication
- Solubility
- Viscosity
- Lipid solubility
- Drug’s pH
- Ionic form
- Molecular size
- Chemical structure
- Surfactants
- Reflex tearing
Subconjunctival and sub-Tenon injection allow drugs to bypass corneal and conjunctival epithelial barriers and enter sclera and intraocular by concentration gradient.

Intraocular injections: intracameral (into the anterior segment) and intravitreal: instantly delivers effective concentration to target site.
**Systemic Administration**

- Blood-ocular barrier: vascular endothelium of retina non-fenestrated with tight junctions
- Choroid and ciliary body sequestered from delivery of systemic meds
- Drugs with high lipid solubility i.e. chloramphenicol penetrates eye much better than penicillin
- Binding of drug with plasma proteins limits free serum levels and must be exceeded
- Bolus IV exceeds the binding capacity of plasma proteins leading to higher intraocular levels of drug when compared with IV drip
# Intracameral and Intravitreal Medication Delivery

<table>
<thead>
<tr>
<th>Route of Administration</th>
<th>Clinical Application</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intracameral</strong></td>
<td></td>
</tr>
<tr>
<td>Acetylcholine</td>
<td>Constrict pupil in intraocular surgery</td>
</tr>
<tr>
<td>Carbachol</td>
<td></td>
</tr>
<tr>
<td>Balanced salt solution</td>
<td>Intraocular surgery, re-formation of anterior chamber</td>
</tr>
<tr>
<td>Viscoelastic material</td>
<td></td>
</tr>
<tr>
<td>Epinephrine</td>
<td>Dilate pupil in intraocular surgery</td>
</tr>
<tr>
<td>Lidocaine (preservative free)</td>
<td>Intraocular surgery, anesthesia</td>
</tr>
<tr>
<td>Methylene blue</td>
<td>Staining of anterior capsule in cataract surgery</td>
</tr>
<tr>
<td>Tissue plasminogen activator (tPA; off-label use)</td>
<td>Assist fibrinolysis of fibrin in anterior chamber and subretinal hemorrhage</td>
</tr>
<tr>
<td><strong>Intravitreal</strong></td>
<td></td>
</tr>
<tr>
<td>Anti-vascular endothelial growth factor (anti-VEGF; eg, bevacizumab, ranibizumab)</td>
<td>Chorioretinal neovascularization, proliferative diabetic retinopathy, diabetic macular edema</td>
</tr>
<tr>
<td>Corticosteroids (eg, triamcinolone acetonide; sustained-release intraocular implants such as dexamethasone in polylactic acid-coglycolic acid matrix and fluocinolone acetonide in a polyvinyl acetate/silicone laminate)</td>
<td>Cystoid macular edema, retinal vein occlusion, posterior uveitis</td>
</tr>
<tr>
<td>Ganciclovir injection or implant</td>
<td>Cytomegalovirus retinitis</td>
</tr>
<tr>
<td>Silicone oil</td>
<td>Vitreoretinal surgery</td>
</tr>
<tr>
<td>Intracocular gases</td>
<td></td>
</tr>
<tr>
<td>Perfluorocarbon</td>
<td></td>
</tr>
<tr>
<td>Various antibiotics</td>
<td>Intraocular bacterial infection</td>
</tr>
</tbody>
</table>
**SUSTAINED RELEASE MEDICATIONS**

- Oral meds: Diamox in sustained release sequel reduces IOP for 20 hours compared with 10 hours for the standard Diamox tablet.
- Ocusert: pilocarpine used in past.
- Surgical implant Ganciclovir for 5-8 months; fluocinolone acetonide steroid.
- Dexamethasone biodegradable polymer matrix (NOVADUR) injection into vitreous cavity Ozurdex for diabetic macular edema.
SUSTAINED DRUG-DELIVERY SYSTEMS

- Encapsulated cell technology
- Nanostructure tethadur: using nanoparticles to protect active molecules and provide sustained delivery; Nano-capsules, Nano-spheres, Nano-suspension and emulsions
- Refillable reservoir
- Refillable pump
COLLAGEN SHIELDS

- Porcine scleral tissue extracted and molded into contact lens-soak shields
- Useful in delivery system prolonging contact time between drug and cornea
- Drugs incorporated into collagen matrix during manufacturing process or absorbed into the shield at rehydration or applied topically while on the eye
- Shield dissolves in 12, 24 or 72 hours

- Poorly tolerated as they are uncomfortable
- Treatment of bacterial keratitis in early stages
**Drug Incorporation into Contact Lens**

- Soak contact lens in drug
- Monomers in contact lens hydrogels with target drugs
- Drug–loaded colloidal nanoparticles into the matrix of the contact lens
- Use molecular imprinting technique wherein contact lens hydrogels are organized for high affinity binding of the drug
**Drug Delivery**

- **Punctal plug** mediated delivery systems
- Core with drug
- Cap with pores which the drug is released
- Advantage: dose reduction, controlled release patient compliance

- **Iontophoresis**: moving charged molecules by electric current; limited by discomfort and ocular damage
Genetically engineered cells designed to overproduce protein of interest

Multi-year implant viability

Encapsulated in nonbiodegradable system

Application for AMD with anti-VEGF, anti-PDGF

ECT with VEGF receptor decoy in clinical trials have demonstrated beneficial decrease in retinal thickness
ENCAPSULATED CELL TECHNOLOGY

Figure 1. Single-chamber (ECT 1/2) and multichamber (ECT 3) configurations.
NANOSTRUCTURED TETHADUR

- Injectable peptide microparticule
- Eggs in and egg carton analogy adsorption of target molecule into customized molecular pores
- Release from matrix over periods of days to months
- Peptide is mixed with Tethadur particles and administered to patient
PRODRUGS

- Inactive derivatives are activated by enzymes inside the eye.
- Ester and amide prodrugs are hydrolyzed by esterase and amidases as they penetrate cornea and conjunctiva.
- Prodrug is more permeable to cornea than active med.
- Prostaglandin analogues such as latanoprost, travoprost, unoprostone (esters prodrugs) and bimatoprost (amide).
COMPOUNDING MEDICATIONS IN OPHTHALMOLOGY

- Pharmacy compounding accreditation board (PCAB) provide evidence of adherence to compounding standards
- State and federal licensing
- Appropriate training aseptic compounding meeting USP guidelines
- www.pcab.org/accredited-pharmacies
- Record lot number of medication and lot number of syringes in patient record
Topical Anaesthesia

- Instillation of LA drops
- Advantages
  - Minimal complications
- Limitations
  - Lack of akinesia
  - Only suitable for uncomplicated cases

TOPICAL ANESTHETICS
Tetracaine, lidocaine gel
# Topical Anesthetics

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Trade Name</th>
<th>Strength</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cocaine</td>
<td></td>
<td>1%–4%</td>
</tr>
<tr>
<td>Fluorescein sodium/benoxinate</td>
<td>Fluress</td>
<td>0.25%</td>
</tr>
<tr>
<td></td>
<td>Flurox</td>
<td>0.25%</td>
</tr>
<tr>
<td></td>
<td>Available generically</td>
<td>0.25%</td>
</tr>
<tr>
<td>Fluorescein sodium/proparacaine</td>
<td>Fluoracaine</td>
<td>0.25%/0.1%</td>
</tr>
<tr>
<td></td>
<td>Flucaine</td>
<td>0.25%/0.1%</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>Topical solution</td>
<td>4%</td>
</tr>
<tr>
<td></td>
<td>Viscous gel</td>
<td>2%</td>
</tr>
<tr>
<td>Proparacaine</td>
<td>Alcaine</td>
<td>0.5%</td>
</tr>
<tr>
<td></td>
<td>Parcaine</td>
<td>0.5%</td>
</tr>
<tr>
<td></td>
<td>Ophthalmic</td>
<td>0.5%</td>
</tr>
<tr>
<td></td>
<td>Available generically</td>
<td>0.5%</td>
</tr>
<tr>
<td>Tetracaine</td>
<td>Altacaine</td>
<td>0.5%</td>
</tr>
<tr>
<td></td>
<td>Tetravisc</td>
<td>0.5%</td>
</tr>
<tr>
<td></td>
<td>Available generically</td>
<td>0.5%</td>
</tr>
</tbody>
</table>
TOPICAL ANESTHETICS FOR SURGERY

- Proparacaine, tetracaine
- Lidocaine 4% for injection can be used topically as well as lidocaine 2% jelly
- Bupivacaine 0.75% (Marcaine) has longer duration of action but increased risk of corneal toxicity
- Intraocular lidocaine: 0.3cc of 1% isotonic nonpreserved lidocaine administered intracamerally. Onset of action 10 seconds. Reduces amount of local and IV sedation needed
LIDOCAINE AND BUPIVOCaina
ANESTHESIA FOR CATARACT SURGERY

Topical lidocaine gel

Intracameral non-preserved 2% lidocaine
TOPICAL, INTRACAMERAL, LOCAL RETROBULBAR, PERIBULBAR EYELID BLOCKS

- Local anesthetics block sympathetic vascular tone and dilate blood vessels
- Epinephrine added to slow vascular absorption
- **Topical**: disrupt tight junctions interfere with corneal repair and metabolism and cannot be used for chronic pain relief

**Lidocaine** (Xylocaine), **Bupivacaine** (Marcaine)

- **Hyaluronidase** increases tissue permeability and increases dispersal of local anesthetic.
- **Hylenex** a recombinant human substitute used instead of hyaluronidase
TOPICAL ANESTHETICS

- Proparacaine (Alcaine, Ophthetic): least irritating, onset of action 15 seconds and lasts 20 minutes
- Benoxinate oxybuprocaine (Fluress, Flurox) similar to proparacaine
- Tetracaine and tetravisc: action and duration similar to proparacaine but with more extensive corneal epithelial toxicity
TOPICAL ANESTHETICS
IV SEDATION

- Patients respond well to intravenous fentanyl and midazolam (Versed) in conjunction with topical and intracameral anesthesia.

- “Vocal local”: calmly provide verbal instructions and reassurance and verbal guidance during the procedure.

- Many patients experience more anxiety when surgery is performed on their second eye.

- Propofol may be added IV in these instances or in general in more anxious patients.
OPHTHALMIC VISCOSURGICAL DEVICES (OVD)
Dispersive to cohesive: Dispersives, cohesives, combination agents, visco-adaptive
Rheological properties determine the classification, include:
- Viscosity
- Viscoelasticity
- Pseudoplasticity
- Surface tension

Building blocks:
- Sodium hyaluronidate (Na HA)
- Chondroitin sulfate (CS)
- Hydroxypropyl methycellulose (HPMC)

The molecular size, weight and concentration of each determine the characteristics of the OVD
COHESIVE VS DISPERSIVE OVDS

Cohesive: higher viscosity: pressurize eye, create space

Dispersive: lower viscosity: coat intraocular structure, retained when injected
OVD EXAMPLES

Dispersive: HPMC

Cohesive (Viscoat) and Dispersive (Provisc) Duo Visc
COHESIVE OVD SODIUM HYALURONIDATE OF VARYING CONCENTRATIONS
Other dispersives:
- Healon D, Viscoat, Ocucoat

Other cohesives:
- Healon, Healon GV, Provisc, Amvisc

Other two syringe systems:
- Duovisc: Viscoat and Provisc; Healon D and H;
  - Healon D and GV
  - Amvisc and Ocucoat

Full spectrum of dispersive and cohesive in one syringe:
- DiscoVisc and Amvisc Plus
New class: super-cohesive viscoelastic and provide protection of dispersives.

VISCO-ADAPTIVE OVD
- Soft-shell technique for cataract surgery
- Combines dispersive and cohesive OVD used simultaneously injecting dispersive first then cohesive

Figure 2. The Arshinoff soft-shell technique is useful to provide the endothelial protection of a dispersive viscoelastic while giving the space creation and pressurizing effects of a cohesive viscoelastic.
# MYDIATICS AND CYCLOPLEGICS

## Table 16-3 Mydriatics and Cycloplegics

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Trade Name</th>
<th>Strengths</th>
<th>Onset</th>
<th>Duration of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenylephrine HCl</td>
<td>AK-Dilate</td>
<td>Solution, 2.5%, 10%</td>
<td>30–60 min</td>
<td>3–5 h</td>
</tr>
<tr>
<td></td>
<td>Aitafrin</td>
<td>Solution, 2.5%, 10%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mydrin</td>
<td>Solution, 2.5%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Neoefrin</td>
<td>Solution, 2.5%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Neo-Synephrine</td>
<td>Solution, 2.5%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Available generically</td>
<td>Solution, 2.5%, 10%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydroxyamphetamine hydrobromide, 1%</td>
<td>Available as powder for compounding</td>
<td></td>
<td>30–60 min</td>
<td>3–5 h</td>
</tr>
<tr>
<td>Atropine sulfate</td>
<td>Atropine-Care</td>
<td>Solution, 1%</td>
<td>45–120 min</td>
<td>7–14 days</td>
</tr>
<tr>
<td></td>
<td>Isopto Atropine</td>
<td>Solution, 1%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Available generically</td>
<td>Solution, 1%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ointment, 1%</td>
<td>Solution, 1%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyclopentolate HCl</td>
<td>AK-Pentolate</td>
<td>Solution, 1%</td>
<td>30–60 min</td>
<td>2 days</td>
</tr>
<tr>
<td></td>
<td>Cyclogyl</td>
<td>Solution, 0.5%–2%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cylate</td>
<td>Solution, 1%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Available generically</td>
<td>Solution, 1%, 2%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Isopto</td>
<td>Solution, 2%, 6%</td>
<td>30–60 min</td>
<td>3 days</td>
</tr>
<tr>
<td>Homatropine hydrobromide</td>
<td>Homatropine</td>
<td>Solution, 6%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Homatropaire</td>
<td>Solution, 6%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scopolamine hydrobromide</td>
<td>Isopto Hyoscine</td>
<td>Solution, 0.25%</td>
<td>30–60 min</td>
<td>4–7 days</td>
</tr>
<tr>
<td>Tropicamide</td>
<td>Mydral</td>
<td>Solution, 0.5%, 1%</td>
<td>20–40 min</td>
<td>4–6 h</td>
</tr>
<tr>
<td></td>
<td>Mydriacyl</td>
<td>Solution, 1%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tropicayl</td>
<td>Solution, 0.5%, 1%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Available generically</td>
<td>Solution, 0.5%, 1%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cyclomydril</td>
<td>Solution, 0.2%/1%</td>
<td>30–60 min</td>
<td>1–2 days</td>
</tr>
<tr>
<td>Cyclopentolate HCl/</td>
<td>Hydroxyamphetamine hydrobromide/</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>phenylephrine HCl</td>
<td>tropicamide</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Paramyd</td>
<td>Solution, 1%/0.25%</td>
<td>20–40 min</td>
<td>4–6 h</td>
</tr>
</tbody>
</table>
PUPIL DILATION FOR CATARACT SURGERY

- Out of the bottle
- Combinations of phenylephrine, cyclogyl and tropicamide from bottle. Solution soaked sponges applied to eye
- Cyclomydryl gel
- Others
DILATING EYE DROPS
DILATING EYE DROPS
DILATING SOLUTIONS

Added to irrigating solution prior to intraocular surgery
Maintains pupil dilation and decreases pain
Phenylephrine and ketorolac (NSAID)
VISION BLUE CAPSULAR STAINING DYE

Inject into eye before capsulorhexis

Stains anterior capsule enhance visualization