# 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 then 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

## ROUTES OF ADMINISTRATION, DRUG DELIVERY SYSTEMS

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

## PERIOCULAR INJECTIONS

- 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 that 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

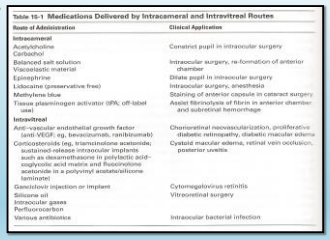


**Table 15-1 Medications Delivered by Intracameral and Intravitreal Routes**

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

## 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

## ENCAPSULATED CELL TECHNOLOGY (ECT)

- 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

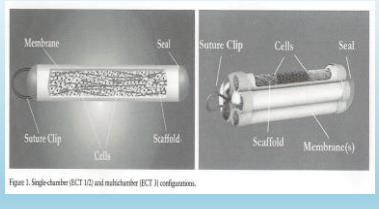


Figure 1. Single-chamber (ECT 1/2) and multichamber (ECT 3) configurations.

## 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 16-23 Topical Anesthetic Drugs

| Generic Name | Trade Name | Strength |
|---|---|---|
| Cocaine | | 1%–4% |
| Fluorescein sodium/benoxinate | Fluress | 0.25% |
| | Flurox | 0.25% |
| | Available generically | 0.25% |
| Fluorescein sodium/proparacaine | Fluoracaine | 0.25%/0.1% |
| | Flucaine | 0.25%/0.1% |
| Lidocaine | Topical solution | 4% |
| | Viscous gel | 2% |
| Proparacaine | Alcaine | 0.5% |
| | Parcaine | 0.5% |
| | Ophthetic | 0.5% |
| | Available generically | 0.5% |
| Tetracaine | Altacaine | 0.5% |
| | Tetravisc | 0.5% |
| | Available generically | 0.5% |

## 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 BUPIVOCAINE



## ANESTHESIA FOR CATARACT SURGERY

**Topical lidocaine gel**


**Intracameral non-preserved 2% lidocaine**

## LOCAL ANESTHETICS

- 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)

Viscoelastics

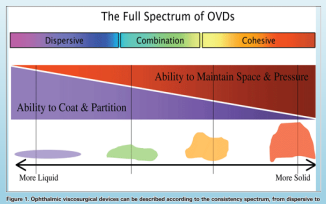



Figure 1. Ophthalmic viscosurgical devices can be described according to the consistency spectrum, from dispersive to cohesive. Dispersive OVDs have a better ability to coat and partition, while cohesive OVDs have a better ability to maintain space and pressurize. Combination products aim to address both ends of the spectrum.

## OVD CONSISTENCY SPECTRUM

Dispersive to cohesive:

Dispersives, cohesives, combination agents, visco-adaptive

## OVD CLASSIFICATION

- 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



## OVD MORE EXAMPLES

- 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



Fig. 3: Healon 5 provides superior protection for the corneal endothelium, according to Robert Osher, MD, of the Cincinnati Eye Institute in Montgomery, Ohio.

## VISCO-ADAPTIVE OVD

New class: super-cohesive viscoelastic and provide protection of dispersives

## ARSHINOFF SOFT SHELL OVD TECHNIQUE

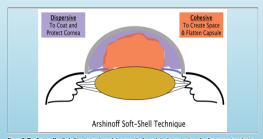



Figure 2. The Arshinoff soft shell technique is useful to provide the endothelial protection of a dispersive viscoelastic while giving the space creation and pressurizing effects of a cohesive viscoelastic.

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

## MYDIATICS AND CYCLOPLEGICS

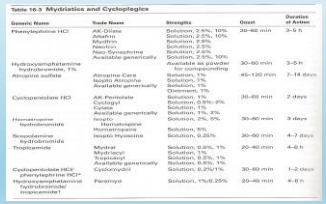


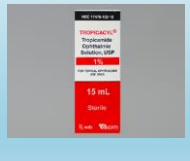
Table 16-3 Mydriatics and Cycloplegics

| Generic Name | Trade Name | Strengths | Onset | Duration of Action |
|---|---|---|---|---|
| Phenylephrine HCl | AK-Dilate<br>Akarin<br>Mydfrin<br>Neo-Synephrine<br>Available generically | Solution, 2.5%, 10%<br>Solution, 2.5%, 10%<br>Solution, 2.5%<br>Solution, 2.5%<br>Solution, 2.5%, 10% | 20–60 min | 3–5 h |
| Hydroxyamphetamine hydrobromide, 1%<br>Atropine sulfate | Atropine-Care<br>Isopto Atropine<br>Available generically | Available as powder for compounding<br>Solution, 1%<br>Solution, 1%<br>Solution, 0.5%<br>Ointment, 1% | 30–60 min<br>45–120 min | 3–5 h<br>7–14 days |
| Cyclopentolate HCl | AK-Pentolate<br>Cyclogyl<br>Cylate<br>Available generically | Solution, 1%<br>Solution, 0.5%–2%<br>Solution, 1%<br>Solution, 0.5%, 2% | 30–60 min | 2 days |
| Homatropine hydrobromide | Isopto Homatropine<br>Homatropine | Solution, 2%, 5% | 30–60 min | 3 days |
| Scopolamine hydrobromide<br>Tropicamide | Isopto Hyoscine<br>Mydral<br>Mydriacyl<br>Tropicacyl<br>Available generically | Solution, 0.25%<br>Solution, 0.5%, 1%<br>Solution, 1%<br>Solution, 0.5%, 1% | 30–60 min<br>20–40 min | 4–7 days<br>4–6 h |
| Cyclopentolate HCl/ phenylephrine HCl* | Cyclomydril | Solution, 0.2%/1% | 30–60 min | 1–2 days |
| Hydroxyamphetamine hydrobromide/ tropicamide† | Paremyd | Solution, 1%/0.25% | 20–40 min | 4–6 h |

## 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**