Pharmacokinetics

- What the body does to a drug
  - Movement of drug into, through, and out of the body
  - Time course of its absorption, bioavailability, distribution, metabolism, and excretion.

Absorption
- Factors
  - Molecular Weight, +/- Charge, pH/pKa, Concentration, Viscosity of Vehicle, Contact Time, Tissue Properties, Elimination, Tear Protein Binding
  - Uncharged, lipophilic, goes through cornea the best

Distribution
- Passive diffusion
  - Most all drugs (use concentration gradient)
- Facilitated Diffusion
- Active Transport

Drug Challenges/Fate

Routes of Ocular drug administration

- Topical
  - Prompt absorption
  - Convenient, economical, safe
  - Limitations: corneal and conjunctival toxicity, nasal mucosal toxicity, systemic side effects from nasolacrimal absorption

- Intraocular Injections
  - Prompt
  - Anterior segment Sx, infections
  - Limitations: Corneal toxicity, intraocular toxicity, relatively short duration of action

- Subconjunctival, sub-Tenon’s and retrobulbar injections
  - Prompt
  - Anterior segment infections, Post-vascular cystoid macular edema
  - Limitations: Local toxicity, tissue injury, globe perforation, optic nerve injury, central retinal artery and/or vein occlusion, direct retinal drug toxicity, with inadvertent globe perforation, ocular muscle trauma, prolonged drug effect
Drug Administration

Ocular Drug Fate
- Drainage into the nasolacrimal apparatus
- Absorption into the systemic circulation by the conjunctival and lid vasculature
- Penetration into the cornea

25% of topical drug concentration is lost from evaporation on installation!


Ocular (Local) Drug Course
- Local (drops, injection, creams)
  - Drug binding to tear proteins
  - Drug eliminated by nasolacrimal drainage
  - Drug metabolism by tear and tissue proteins
  - Diffusion across the cornea and conjunctiva

Oral Drug Course
- Some absorption into bloodstream in the stomach, but most goes to the intestine
- Intestine: Drug enters bloodstream
- Drug binds to appropriate receptor and metabolizes.
- Drug is eliminated from the body through chemical reaction

Drug Need
- Anterior chamber
- Posterior chamber
- Delivery challenges
Drug Need

- Corneal Transmissibility

Drug at Equilibrium

Tear film buffers drug to a pH of 7.4

Drug at Equilibrium

pH of tear film 7.4

Drop pH is 6

Tear film buffers drug to a pH of 7.4

The non-ionized (lipid soluble) portion will penetrate the epithelium

Drug reorganizes to Equilibrium

The non-ionized (lipid soluble) reaches the aqueous humor

Ionized portion (water soluble)
Drug Absorption

- Most ocular drugs are formulated as weak bases because of more non-ionized portions of the drug reaching the aqueous humor
  - Better penetration
  - Better bioavailability

Lipid Soluble (Lipophilic) = Non-Ionized

Pharmacokinetics

- Metabolism
  - Drug Binding
  - Ciliary Body
    - Major ocular source of metabolizing enzymes
  - Prodrugs
    - Must be metabolized to be active
- Elimination
  - Retinal Vessels -> Uveal Vessels -> Direct outflow pathway

Drug Absorption FYIs

- BAK and drug penetration
- Corneal CXL and drug penetration
  - Corneal cross-linking with ultraviolet-A and riboflavin results in a statistically significant reduction in corneal permeability.
- Diseases such as diabetes can result in increased corneal cross-linking through the sustained elevation of glucose levels.

Why use Prodrug?

- Improve patient acceptability
- Alter and improve absorption
- Alter biodistribution
- Alter metabolism
- Alter elimination
Prodrug

- Nepafenac
  - Ophthalmic suspension used to reduce pain and swelling after cataract Sx
  - Penetrates the cornea and is converted by ocular tissue hydrolases to amfenac

- Valacylovir
  - Oral antiviral used to help with herpes infections (i.e. shingles)
  - Penetrates the cornea and is converted by ocular tissue hydrolases to amfenac

Distribution

- Melanin binding of certain drugs is an important factor in some ocular compartments.
  - i.e. mydriatic effect of a adrenergic receptor agonist (Tropicamide)

Drugs in Clinical Use

- If Kidney is 10% below normal function will not excrete most antibiotics
**Local Anesthetics**

- **800 A.D. First documented use**
- Benzoic acid ester
- Led to synthesis of procaine 1905, then lidocaine 1940’s for WWII

**Injectable Anesthetics**
- Lidocaine (Xylocaine) 1%
  - with or without epinephrine 0.5mg to 1mg
- Bupivacaine

**Topical Anesthetics**
- Ester
- Tetracaine
- Proparacaine
- Lidocaine (Xetal)
Local Anesthetics

Topical Anesthetics
- Esters
  - Tetracaine
  - Benoxinate
    - w/fluorescein or fluoroexc
  - Proparacaine
- Amide
  - Lidocaine (Akten)

All have rapid onset of anesthesia beginning within 13-30 second
Duration: 15-20 mins


Side Effects
- Allergy
  - Allergic reactions to local anesthetics occur almost exclusively to those with ESTER linkage (topicals, except Akten)
  - Literature reports demonstrate that cross-sensitivity reactions are rare between proparacaine (Ophthetic®, Alcaine®), an ester, and other ester anesthetics.
- Stinging
- Burning
- Conjunctival Redness
- Corneal Toxicity


Contraindications
- Known hypersensitivity

Mydriatics, Mydriolytics, and Cycloplegics

Parasympathetic (cholinergic system)
- Leaking, oozing

Sympathetic (adrenergic system)
- Fight or flight

Cholinergic stimulation in the eye (parasympathetic)
- Drug BINDS to receptor
  - Effects
    - Miosis
    - Increase aqueous drainage
    - Lacrimation

Autonomic Nervous System
### Autonomic Nervous System

#### Drugs
- Pilocarpine 0.25% - 10% (4%)

#### Indications
- POAG?
- Acute angle closure

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#### Cholinergic Antagonist (parasympathetic inhibitors)
- **Drug** BLOCKS receptor  
  - **Effects**
    - Mydriasis
    - Blurred Vision
    - Dry Eye

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#### Anti-Cholinergic Agents

<table>
<thead>
<tr>
<th>Mydriatics and cycloplegics</th>
<th>Mydriasis</th>
<th>Cycloplegia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Strength (hr)</td>
<td>Maximal (min)</td>
</tr>
<tr>
<td>Atropine sulfate (multiple)</td>
<td>1</td>
<td>30–45</td>
</tr>
<tr>
<td>Benoxinate hydrochloride (multiple)</td>
<td>0.5</td>
<td>10–20</td>
</tr>
<tr>
<td>Naphazoline hydrochloride (multiple)</td>
<td>1</td>
<td>40–60</td>
</tr>
<tr>
<td>Cyclopentolate (multiple)</td>
<td>0.5–1</td>
<td>30–60</td>
</tr>
<tr>
<td>Tropicamide (multiple)</td>
<td>0.5–1</td>
<td>20–40</td>
</tr>
<tr>
<td>Pseudoephedrine hydrochloride (multiple)</td>
<td>0.5–1</td>
<td>20–60</td>
</tr>
</tbody>
</table>

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#### Pregnancy and Dilation

- American Academy of Ophthalmology  
  *All mydriatic/cycloplegic agents are categorized as Pregnancy Category C*

- The potential effects of topical anesthetic and dilating drops in the pregnant patient are unknown, and the routine use of these agents should be avoided unless indicated to evaluate a new symptom or monitor a specific disease.

- When necessary, their use is generally thought to be safe, especially with punctal pressure for 2 minutes after administration.

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#### Adrenergic System
- **Effects**
  - Increased BP/HR
  - Mydriasis
  - Lid elevation
  - Decreases aqueous fluid production
**Autonomic Nervous System**

**Adrenergic Agonist Drugs**
- Phenylephrine 2.5%, 10%
- Cocaine 2-10%
- Hydroxyamphetamine
- Combinations
  - Paremyd (1% hydroxyamphetamine + 0.25% tropicamide)
  - Cyclomydril (0.2% cyclopentolate + 1% phenylephrine)

**Adrenergic Antagonist Drugs (adrenergic blocking agents)**
- Dapiprazol 0.5%
- Rev-eyes
  - *Reversal Drops*

**Ophthalmic Dyes**

**Sodium Fluorescein (NaFl)**
- Fluorescein mostly absorbs light of wavelengths between 485 and 500 nm (Blue light spectrum)
- Used to show areas of desiccation or poor wetting
- Tear Break-up Time (TBUT) of < 8 sec is abnormal
- Bron et al.
  - Desiccating environmental stress from wind, low ambient humidity (plane), and decreased blinking exacerbates tear evaporation.
  - Looking upward or straight ahead is associated with 2.5 to 3.4 times greater evaporative tear loss than a downward gaze.

**Corneal and Conjunctival Staining**

- Rose Bengal and Lissamine Green
  - Stain damaged and devitalized conjunctival cells
  - These cells lack protection by precorneal tear film and mucus
Ocular Adverse Drug Reactions from systemic medications

Hydroxychloroquine
- Retinopathy
  - MA: ?
  - Drug affects the metabolism of retinal cells and also binds to melanin in the RPE
- New dosing

Drugs Causing Dry Eye
- Of the top 100 best-selling systemic drugs in the US in 2009, 22 proved to possibly cause dry eye secondary to decreased tear production, altered nerve input and reflex secretion, inflammatory effects on secretory glands or direct irritation effects through secretion into the tears.
  

Let's Get In Touch
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THANK YOU!