Advanced Ophthalmic Pharmacology:
A Practical Approach

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- I have no financial interests in this presentation
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Overview of this hour

- Drug delivery – the Big Picture
- Autonomic nervous system
- Medications and clinical scenarios
  - Diagnostic drugs
  - Glaucoma drugs
  - Antibiotics
  - Anti-inflammatory agents
  - Anesthetics
  - Lubricants
- Ocular side effects of systemic medications
  (generic names only used in this presentation)

Drug Delivery: the inside story

- Concentration
- Tonicity and tolerance
- Sterility
- Penetration
- Application technique
- Compliance
- Agonist and antagonist actions

Drug Delivery: How to get the drop in(side) the eye

Concentration
- Only a small volume applied, so drops are highly concentrated medications
- Example: atropine 1% drop = 0.5 mg, the cardiac (ACLS) resuscitation dose
- Antibiotic eye drops are highly concentrated, may work even when bacteria “resistant”
- No discussion of dosage due to time limits
Drug Delivery: How to get the drop inside the eye

Tonicity & tolerance (“tear like”)
- ideal 0.9% saline and pH 7, feels like tears
  - Concentrated drop may be hypertonic / stingy
  - Reflex tearing and washout (refrigerate)
    - Fuchs’ patients and hypertonic drops
- Solution vs. suspension (shake before use)

Drug Delivery: How to get the drop inside the eye

Sterility
- Eyedrops with replaceable caps manufactured with preservatives (fewer bacteria, more toxicity!)
  - Non-preserved medications are autoclaved, and / or passed through micro-filters, then sealed with non-replaceable cap (ampule)
  - Recent small epidemic of fungal corneal infections from contaminated contact lens solutions

Drug Delivery: How to get the drop inside the eye

Penetration through the cornea
- cornea is (oil/water/oil) “sandwich”
- little medication to posterior segment
- benzalkonium Cl preservative – irritant (increases intraocular carbachol level 17x!)
- Dark iris color reduces mydriatic action
- Tonometry or corneal abrasion / ulcer
  - Both drops and contact loosen junctions

Drug Delivery: How to get the drop inside the eye

Delivery technique
- Topical use is drops or ointments
  - Drops: easy to instill, but eye contact brief
  - Ointment: much harder to administer, but longer contact time with eye
- Slow release reservoirs:
  - Ocusert, collagen shields, Timoptic XE
Delivery technique

- Drop size is 50 microliters, but tear volume is only 10 microliters – only use one drop!
- Tear turnover rate ~ 16%/min
  - therefore from original drop: only a small % left at 5 minutes
  - Eyelid closure increases concentration, comfort, and contact time (equal and cleaner than manual NLD occlusion)

Injections
- Subconjunctival: drug surrounds sclera to reach macula and posterior segment
- Anterior chamber or vitreous injection
- Systemic delivery (pills / IV) diluted throughout body. May have undesirable side effects on other systems (heart, GI, brain)

Compliance

- Major issue in glaucoma treatment
  - Higher dosage frequency, poorer compliance
  - You can help!
  - Standardized bottle top color scheme

- Other terms you may hear –
  - Agonist: helps nerve or muscle do job
  - Antagonist: works against nerve or muscle
**Autonomic Nervous System**

- Unconscious “maintenance” functions
- Sympathetic and parasympathetic
- Adrenergic and cholinergic
- ‘mimetic or ‘lytic
- Accommodation and Cycloplegia
- Mydriasis and Miosis

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**Diagnostic Agents: Sympathetic**

*“flight (fright) or fight”: sympathomimetic*

- ‘Mimic’ adrenalin (norepinephrine) action; dilate pupil, vasoconstriction, race the heart
- Alpha and beta receptors; stimulators (“agonists”) and blockers (antagonists)
- Neosympinephrine (Phenylephrine) 2.5 and 10%; dilates pupil, has no effect on accommodation
  - Additive to Mydriacyl/ Cyclogel
  - Can differentiate conjunctivitis from scleritis
- Diagnostic Agents: Sympathetic
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**Sympatholytic**

- **Antagonists**
  - Dapiprazole (Rev-eyes) is alpha receptor blocker; it reverses mydriasis from phenylephrine
  - Not as useful for reversing cycloplegia from parasympatholytics
  - Beta receptor blockers are glaucoma agents (like Timoptic)
**Diagnostic agents: Parasympathetic**

- **Parasympathetic system**
  - "old man sitting in rocking chair on his front porch after a big meal"

- **Parasympathomimetic drugs** stimulate cholinergic (acetylcholine) action
  - directly
  - indirectly
    - Blocking metabolism of acetylcholine, extending its action; constrict pupil, accommodate (muscle spasm)

**Parasympatholytics**

- **Parasympatholytics**: antagonists block the action of acetylcholine; cause pupillary dilation and paralyze accommodation
  - Dilating agents / cycloplegic agents (atropine, mydriacyl, cyclopentolate)
  - Red caps = RED means STOP for acetylcholine, or “anti-cholinergic”

**Parasympathomimetic**

- **Parasympathomimetic**: agonists that ‘mimic’ effect of acetylcholine, Green caps > (GREEN means GO for acetylcholine)
- Miosis and glaucoma treatment
- also used to treat accommodative esotropia
- Miochol, Miostat, pilocarpine, carbachol, phospholine iodide

**Onset and Duration**

- **Mydriatics and cycloplegics**:
  - Mydriacyl – 15 min – 6 hours
  - Cyclogel – 30 min – 12 hours
  - Homatropine – 30 min – 2 days
  - Scopalamine – 30 min – 3 days
  - Atropine – 60 min – 2 weeks

- Also useful for reducing inflammation by keeping iris paralyzed
Parasympatholytics

- Systemic toxicity – too much absorbed into body
  - “mad as a hatter, hot as a hare, red as a beet, dry as a bone”
  - Irritability, confusion, seizures / fever, tachycardia / flushing
  - Antidote is physostigmine (eserine) 0.25 mg subcutaneously

Clinical Problem

- Premature infant in NICU, 6 weeks old, birthweight 900 grams, supplemental O2
- Rule out retinopathy of prematurity
- Are you going to be concerned about how much medication this baby gets?

Glaucoma

- POAG: primary open angle glaucoma
- A chronic, asymptomatic disease, no cure, costly, requires constant attention
- All factors foster noncompliance
- Motivation and empowerment of patient

  "Frequently the only symptoms of glaucoma are the ones that we give the patient."

Clinical Problems

- Elderly man with POAG and emphysema
- Middle-aged woman with POAG and heart disease with high cholesterol
Medical treatment of glaucoma

- Decrease production = aqueous suppressants
  - beta-blockers
  - alpha-2-agonists
  - carbonic anhydrase inhibitors

- Increase drainage/outflow (trabecular meshwork and uveoscleral)
  - miotics
  - adrenergic agonists
  - prostaglandins

Beta-blockers

- Nonselective: blocks both beta receptors (types 1 and 2) = may have effects on heart and lungs
  - timolol, levobunolol, metipranolol, carteolol

- Selective: block only beta-1 = heart, not lungs (relatively) betaxolol
  - safer, but not as effective in IOP reduction (by 2 mmHg)

Beta-blockers

- In use since 1978, still very popular
- Twice daily dosing (except only once daily for Timoptic XE, which has polysaccharide vehicle that forms a gel, so it persists in the tears)
- First 2 weeks marked IOP drop (‘honeymoon’), then IOP levels out at about 30% reduction
- Medication binds to iris; takes 4 weeks to wash out this ‘depot’ after stopping use of medication

Beta-blockers

- Advantages: minimal burning, stinging
- Systemic side effects can be severe (and fatal)
  - may cause bronchospasm or bradycardia
  - can hide hypoglycemic symptoms in diabetic
  - lethargy, confusion, depression, impotence
  - May be reduction in HDL (‘good’ cholesterol)
    - less with carteolol
Clinical Problem

- 75 y.o. with newly diagnosed POAG, heart disease and long smoking history
- Now you see how his eye drops can affect his general health

Clinical Problem

- 35 y.o. lady with pigmentary glaucoma and red, itchy, watering eyes
- What glaucoma treatment might make her symptoms worse?

Alpha-2-agonists

- apraclonidine
  - initially used to prevent IOP spikes post YAG / ALT
  - tachyphylaxis = can lose effect over time
  - conjunctival blanching, lid retraction, allergic conjunctivitis, dry mouth
- brimonidine used three times daily
  - similar to apraclonidine; less allergic conjunctivitis
  - also drowsiness, fatigue, reduced blood pressure
  - available in combination with timolol (Combigan)

Carbonic anhydrase inhibitors

- Oral agents:
  - acetazolamide and methazolamide - “water pills”
- Oral or IV treat both eyes, but have many systemic side effects, which include...
**Systemic side effects**

- Tingling of fingers, toes, lips (common)
- Metallic taste; beverages taste funny
- GI upset; nausea, diarrhea (take with meals to minimize these symptoms)
- Malaise, depression, loss of libido
- Kidney stones
- Aplastic anemia (can be fatal)

**Topical c. a. inhibitors**

- Dorzolamide, not as potent as oral acetazolamide in IOP reduction
- Fewer systemic side effects
- Burning, stinging, bitter taste (lid closure may reduce this)
  - Brinzolamide
  - Combination: timolol / dorzolamide

**Miotics**

- Resemble acetylcholine:
  - pilocarpine, carbachol, phospholine iodide
  - Miochol™, Miostat™ – intraoperative use
- Increase aqueous humor outflow through the trabecular meshwork
- Contract ciliary body muscle, which stretches the meshwork to open wider

**Miotics**

- Potency: P.I. > carbachol > pilocarpine
- Miochol™: intraocular use--rapid onset and short duration
- Miostat™: intraocular use--not as “stat”, but lasts longer- better for IOP reduction
Miotics

- Pilocarpine: peak action 2 hours, lasts 8 hours; QID drug, compliance challenge
- Pilogel™: qhs, IOP reduction for 18+ hr, good for increasing compliance
- Ocusert™ (P-20, P-40): in place 5-7 days
- Carbachol: TID
- Phospholine iodide: BID (R.D. risk)

Side effects: miosis (problems with cataracts), brow ache (muscle spasm)
- Cataractogenic, breakdown of blood eye barrier (stop prior to surgery)
- Iris cysts in kids
- Induced myopia
- Angle closure, retinal detachments
- Tolerated well by pseudophakes

Clinical Problem

- 85 y.o. can’t remember meds, complains of frontal headaches
  - ...has small pupils and anterior cataracts

Adrenergic agonists

- Dipivefrin:
  - Pro-drug--converted to epinephrine in the cornea
  - Dipivefrin penetrates cornea 17x better than epinephrine would
- Decrease IOP by increasing outflow
Adrenergic agonists

- Side effects - very common, especially with epinephrine
- Increased blood pressure and heart rate/arrhythmia
- Frequent allergic conjunctivitis; mydriasis; adrenochrome deposits; rebound hyperemia - these patients often have red eyes; cystoid macular edema

Prostaglandins

- IOP reduction as good or better than timolol
- Once a day (bedtime); increase uveoscleral outflow and compliance
- Latanoprost, bimatoprost, travoprost, unoprostone

Latanoprost

- Side effects: minimal stinging/burning (similar to timolol)
- Conjunctival hyperemia
- Iris pigmentation (“tan with Xalatan™”) — two-toned iris, darker inside — at risk
- Increase number of eye lashes
- Cystoid macular edema
# Hyperosmotics

- Useful in acute glaucoma attack
- Significant side effects – use with care

- Oral
  - Glycerin
  - Isosorbide
- IV
  - Mannitol
  - Urea

# Antibiotics

- Antibacterials
- Antivirals
- Antifungals
- Antiamoebics

- Bacteriostatic vs. bacteriocidal
  - Minimum inhibitory concentration
- Sensitivity vs. resistance
  - PPNG, VRE, MRSA, MDR TB
- Toxicity vs. allergy
Anti-bacterials

- **Penicillins**
  - Penicillinase-resistance, reduced use
- **Cephalosporins**
  - Four generations so far
  - cefazolin, ticarcillin “fortified” gtts
- **Fluoroquinolones – most popular**
  - ciprofloxacin, norfloxacin, ofloxacin, levofloxacin, gatifloxacin, moxifloxacin
  - Recent FDA warning about tendon rupture after oral use, not ophthalmic

Sulfa

- **Sulfonamides**: broad spectrum, but allergy common, often used in 1970’s
- Sulfacetamide, sulfisoxazole

Clinical Problem

- Hives and shortness of breath after taking medication
- Stevens-Johnson syndrome

Clinical Problem

- Rosacea and Meibomitis
Tetracyclines

- Oral tetracycline “off-label” – for non-antibiotic effect on sebaceous glands
- Also doxycycline, minocycline
- Can stain permanent teeth of fetus and children under age of 7
- Take on empty stomach, sunburn risk
- Higher medication level in eye from ointment than from drops

Macrolides: erythromycin

- Allergy rare or non-existent
- No sting, good for pediatric patients
- Sebaceous effects, too

Chloramphenicol

- Broad spectrum, under-utilized
- Higher medication level in eye from ointment than from drops
- History of toxicity (aplastic anemia) vs. coincidence

Aminoglycosides

- Wide spectrum of activity
- Casually abused by health care providers
- Auditory, renal, and retinal toxicity
- Gentamicin, Tobramycin
- Both can be mixed as “fortified”
- Neomycin – only as combination
- Vancomycin, amikacin – only “fortified”
  - VRE (vancomycin-resistant enterococcus)
### Topical Antibacterials

- Polymixin B: only available as combo
- Trimethoprim: combo with Polymixin
- Bacitracin: low toxicity, available as ung only, 500 “units” per gm
- Neosporin™: neomycin, polymixin B, bacitracin combo – also in many steroid/antibiotic combinations

### Clinical Problem

- Young man with lesions on face and painful eye

### Antivirals

- Only useful for Herpes, not other viruses like epidemic keratoconjunctivitis (EKC)

- Topical: Vidarabine ung, Trifluridine gtts

- Orals: acyclovir, famciclovir
  - Europeans have acyclovir in ung form; we have the FDA instead

- Intravitreal: foscarnet, ganciclovir, valganciclovir, fomivirsen
Clinical Problem

- Corneal abrasion from paper cut at office

Antifungals

- Fungus: molds and yeasts
- Immunosuppression often contributory
- Natamycin, Fluconazole, Amphotericin B
- Oral: flucytosine, fluconazole, ketoconazole, itraconazole, clotrimazole, miconazole

Clinical Problem

- Merchant Marine who stores soft contact lenses in tap water, now with painful eye

Antiamoebics

- Acanthamoeba – cysts and trophozoites
- Pool cleaner - polyhexamethylene biguanide (PHMB) 0.02%
- Neosporin, Miconazole, chlorhexidine
- Propanidine (Brolene™): ‘compassionate use’ from CDC in Atlanta
Anesthetics

- Stop nerve conduction by blocking sodium channels in nerve cell wall
- Many uses: tonometry, gonioscopy, foreign body removal, suture removal, evaluating a painful eye, corneal scrapings for cultures, cataract surgery
- Prototype (1884): cocaine (also mydriatic)

Topical Anesthetics

- Proparacaine: rapid onset, least irritating
- Tetracaine: slower onset, longer duration, more corneal toxicity and bacteriostatic
- Benoxinate: combined with fluorescein

Regional Anesthetics

- Lidocaine: topical or injectable
  - with epinephrine (causes vasoconstriction - prolongs effect)
  - retrobulbar; lasts 1-2 hours
  - topical cataract surgery
  - preservative-free can be used intraocularly

- Bupivacaine: topical or injectable
  - Topical for cataract surgery, preservative-free form, less corneal toxicity
  - Retrobulbar: lasts 6-8 hours
Clinical Problem

- Topical anesthetic agents are subject to abuse, often by health care personnel; do not dispense, watch out for sticky fingers!

- Associated with epithelial toxicity, role of preservatives?

Clinical Problem

- Corneal ulcer needs scraping for culture
- Consider proparacaine (not Tetracaine!), because it is not bacteriostatic
- May choose longer acting Tetracaine for foreign body removal

Clinical Problem

- Most cataract surgery now done under topical anesthetic alone

- Historically, retrobulbar block used; typical mix is Lidocaine, Marcaine, Wydase (an enzyme that helps the anesthetic agents to spread out in tissue)
**Fluorescein**
- Strips - developed due to Pseudomonas contamination of solutions
- Solution - single dose dropper
- Intravenous - retinal angiography
  - Side effects: nausea, vomiting (Rx Benedryl), yellow skin and urine, anaphylaxis
- Rose bengal, lissamine green, isocyanate green – other ophthalmic dyes in use

**Goniosol™**
- High concentration methylcellulose (2.5%)
- Used for contact lens examinations
  - Gonioscopy
  - Retinal (usually macular) exam
- Goniosol protects cornea from abrasion while creating better optical conditions

**Clinical Problem**
- Pterygium has recurred after surgery

**Antimitotics**
- Antibacterials that are very toxic
- Used in chemotherapy, glaucoma surgery
- Some use during or after LASIK (!)
- Mitomycin C, Thiotepa, 5-Fluorouracil
Clinical Problem

- Young lady with chronic uveitis and iris synechiae (adhesion to lens)

Anti-inflammatories

- Includes both steroids and non-steroidal anti-inflammatory agents (NSAIDs)
- Relative potencies, solubility issues (“shake it”) 
- Frequent effect on intraocular pressure 
- Prednisolone, fluorometholone, loteprednol, dexamethasone, rimexolone
- Medrysone - good for surface disorders only 
- Cyclosporine A – formerly dilute IV, now in Restasis

Steroid side effects

- Glaucoma (sometimes transient) 
- Cataract (posterior subcapsular) 
- Risk of infection – HSV most worrisome 
- Ptosis (also sometimes resolves) 
- Scleral melting 
- Oral steroids – too many to mention!
### NSAIDs

- Non-steroidal anti-inflammatory agents
- Less potent than steroids
- May be equally effective in some cases
- Biochemical effect related to aspirin
- Useful for cystoid macular edema, seasonal allergy, improving dilation during surgery
- Diclofenac, flurbiprofen, ketorolac

### Clinical Problem

- Eyes occasionally red at smoky parties

### Decongestants

- Vasoconstriction of conjunctival vessels
- May be useful for differentiating episcleritis from conjunctivitis
- OTC versions – rebound hyperemia
- Naphazoline, tetrahydrozoline, phenylephrine, oxymetazoline

### NSAIDs

- Four chemical classes
  - When one seems to be losing its effect, often possible to get relief with another
- Salicylates
- Indoles
- Phenylalkanoic acids
- Pyrazolones
Clinical Problem

- Eyes itch during pollen season

Antihistamines

- Either block histamine release or stabilize mast cells, which contain histamine, or both
- Dramatic effects of eye rubbing

Anti-histamines:
- Emedastine
- Mast cell stabilizer (takes several weeks to kick in)
  - Lodoxamide, pemirolast, cromolyn, medocromil
- Both
  - olopatadine; epinastine; azelastine
- Steroids, ketotifen, and ketorolac also useful

Clinical Problem

- Eyes overflow with tears when reading

Lubricants

- Viscosity vs. vision
- Preservatives or non-preserved drops
- Blephritis, systemic medications
- Menopause (testosterone)
- Methylcellulose, polyvinyl alcohol, lanolin, petrolatum, propylene glycol, oral pilocarpine
- Hyperosmotics (lubricant value only)
Side Effects

Systemic medication effects on the eye
- Flomax™, diuretics, BCPs, aspirin, steroids
- Photos:
  - ethambutol
  - amiodarone
  - chloroquine

White optic nerve (atrophy) from treatment of TB

Deposit in front layer of cornea: amiodarone

“whorl” appearance due to migration of surface cells

“Bulls eye” lesion in macula from chloroquine toxicity over prolonged use

“aspirin” appearance
Miscellaneous Agents

- Extra credit only!
- Adhesives (“off-label”)
- Alpha chymotrypsin
- Antihelminthics
- Chelating agents
- Betadine 5%
- Antioxidants

Information Sources

- Your doctor!
- AMA Drug Evaluations
- Ophthalmic Drug Facts
- PDR for Ophthalmology (first 50 pages)
- Not so good: Internet, rumor, PDR

QUESTIONS?