Advanced Ophthalmic Pharmacology: A Practical Approach

Maj Vasudha A. Panday, M.D.
Wilford Hall Medical Center
San Antonio, Texas

Financial Disclosure

- 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

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)

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

Penetration through the cornea
- Cornea is (oil/water/oil) "sandwich"
- Little medication to posterior segment
- Benzalkonium CI preservative - irritant (increases intraocular carbachol level 17x!)
- Dark iris color reduces mydriatic action
- Tonometry or corneal abrasion / ulcer
- Both drops and contact loosen junctions

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)

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
**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)
  - Neosynephrine (Phenylephrine) 2.5 and 10%; dilates pupil, has no effect on accommodation
    - Additive to Mydriacyl / Cyclogel
    - Can differentiate conjunctivitis from scleritis

**Sympatholytic**

- Antagonists
  - Dapiprazole (Rev-eyes) is alpha receptor blocker; it reverses mydriasis from phenylephrine
  - Not as useful for reversing cycloplegia from parasympathomimetics
  - 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)

**Parasympathetic**

- 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

**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"

**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

- 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

- 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)

Miotics

- 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

adrenochrome deposits
**Hyperosmotics**

- Useful in acute glaucoma attack
- Significant side effects – use with care
- Oral
  - Glycerin
  - Isosorbide
- IV
  - Mannitol
  - Urea

**Antibiotics**

- Antibacterials
- Antivirals
- Antifungals
- Antiamoebics

**Antibiotics**

- 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

**Clinical Problem**

- Hives and shortness of breath after taking medication
- Stevens–Johnson syndrome
Sulfa
- Sulfonamides: broad spectrum, but allergy common, often used in 1970’s
- Sulfacetamide, sulfisoxazole

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 (PHBG) 0.02%
- Neosporin, Miconazole, chlorhexidine
- Propanidine (BroleneTM): ‘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

Regional Anesthetics

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

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

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

Clinical Problem

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

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!

Antimitotics

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

Anti-inflammatory

- 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
**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

**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

Deposit in front layer of cornea: amiodarone

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