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JCAHPO Regional Meetings
2017
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

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 in(side) 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 in(side) 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)

Delivery technique

- 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

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/Cyclogyl
      - 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 parasympathomlytics
    - 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
  - Scopolamine – 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
- **Miocol\textsuperscript{TM}**: intraocular use—rapid onset and short duration
- **Miostat\textsuperscript{TM}**: intraocular use—not as “stat”, but lasts longer—better for IOP reduction

### Clinical Problem

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

### Clinical Problem

- **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**

### Miotics

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

### 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, tafluprost, 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
Antibiotics

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

Anti-bacteria

- Penicillins
  - Penicillinase-resistance, reduced use
- Cephalosporins
  - Four generations so far
  - Cefazolin, ticarcillin “fortified” gtt's
- Fluoroquinolones – most popular
  - Ciprofloxacin, norfloxacin, ofloxacin, levofloxacin, gatifloxacin, moxifloxacin
  - Recent FDA warning about tendon rupture after oral use, not ophthalmic; possible risk of RD

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
- Oral: acyclovir, famciclovir
  - Europeans have acyclovir in ung form; we have the FDA and “big PHARMA”
  - Ganciclovir ointment now available, but cost is astronomic
- Intravitreal: foscarnet, ganciclovir, valganciclovir, fomiviren
Clinical Problem

- Corneal abrasion from paper cut at office

Antifungals

- Fungus: molds and yeasts
- Immunosuppression often contributory
- Natamycin, Fluconazole, Amphotericin B
- Oral: flucytosine, fluconazole, ketconazole, 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 (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

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 (1)
- 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
- Xiidra (lifitegrast): newly approved for dry eye

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, fluribiprofen, 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
- Blepharitis, 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
  - Others:
    - Ethambutol
    - Amiodarone
    - Chloroquine
White optic nerve (atrophy) from treatment of TB

“aspirin” appearance

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

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

QUESTIONS?

Miscellaneous Agents
- Adhesives (“off-label”)
- Alpha chymotrypsin
- Antihelminthics
- Chelating agents
- Betadine 5%
- Antioxidants