ALL YOU NEED TO KNOW ABOUT OCULAR PHARMACOLOGY

Brad Genereux, OD

Financial Disclosures

- No disclosures

Outline

- Importance
- Instillation
- Identification
- Autonomic Nervous System
- Adrenergic and Cholinergic Agents
- Mydriatics, Miotics, and Cycloplegics
- Glaucoma Medications
- Corticosteroids
- NSAIDs (non-steroidal anti-inflammatory)
- Anti-Allergy
- Anti-infective (bacterial, viral, fungal)
- Systemic Effects of Ocular Medications
- Ocular Effects of Systemic Medications
- Self-Test Questions

Importance

- Know drugs you’re administering to patient
- Patient education
- Reactions
- Triage

Importance

- For the COA/COT/COMT
- Old (pre-2013):

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- New (post -2013):

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Instillation

- Essential Steps:
  - Wash Hands with Soap and Water or hand sanitizer
  - Check dropper tip for imperfections
  - Avoid touching dropper tip to any surface
  - Tilt head back, pull down lower eyelid with one hand
  - With other, hold dropper close to eye without touching it, brace hand on face if necessary
  - While looking up squeeze bottle so a single drop dispenses
  - Drop is successfully instilled if it lands anywhere on eye or in pocket created with lower lid
  - Close eye gently, and apply pressure with hand to tear duct
  - Dab eye (closed) with tissue
  - Wash hands
  - If instilling more than one drop wait at least 5 minutes between drops

Identification

- ALWAYS read label
- Coloured top for different drops
  - Red - cycloplegic/mydriatic
  - Green - miotics
  - Tan - antibiotics
  - Pink/white - steroids
  - Gray - NSAIDs
  - Yellow - beta blockers
  - Purple - alpha agonist
  - Teal - prostaglandin analogues
  - Orange - CAIs
  - Blue - Combo glaucoma
- Colours do NOT show concentration

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Nervous System

- Basic Neuron/Neurotransmitter

Autonomic Nervous System

- Drugs can either enhance or depress a given system
- Mimetic – “mimics” system, increases activity
- Lytics – decrease activity
- Sympathomimetic – increase sympathetic activity
- Sympatholytic – decrease sympathetic activity
- Parasympathomimetic – increase parasympathetic activity
- Parasympatholytic – decrease parasympathetic activity

Autonomic Nervous System

- Regulates involuntary actions of body
- Consists of two parts:
  - Sympathetic – primarily excited state of body
    - “Flight of fight”
  - Parasympathetic – primarily rest and relaxation
    - SLUD
- Two systems oppose and work together for dynamic homeostasis
- Sends messages by way of nerve impulse (action potential) using neurons and neurotransmitters

Autonomic Nervous System

- Sympathetic:
  - Pre-ganglionic Neuritic

Nucleus → Ganglion → Effector Organ

- Parasympathetic:
  - Pre-ganglionic Nicotinic

Nucleus → Ganglion → Effector Organ

- Sympathetic Nervous System
  - Tends to have excitatory and physiologic effect
    - But excitatory and inhibitory signals to an excitatory system
  - Fight or flight response
    - Pupils dilate
    - Breathing increases, bronchioles dilate
    - Heart rate increases, increase contraction, vasoconstriction to skin and digestive organs

- Autonomic Nervous System
  - Nucleus
  - Ganglion
  - Effector Organ
  - Pre-ganglionic Neuritic
  - Nicotinic
  - Muscarinic (M1, M2, M3, M4, M5)
  - Adrenergic (α1, α2, β1, β2)
  - Norepinephrine
  - Epi/norepi

- Post-ganglionic Neuritic
  - Tends to have excitatory and physiologic effect
Autonomic Nervous System

- Sympathetic:
  - Pre-ganglionic 
  - Nicotinic 
  - Adrenergic $(\alpha_1, \alpha_2, \beta_1, \beta_2)$
  - Post-Ganglionic 
  - Effector Organ 
  - Neurotransmitter

- Parasympathetic:
  - Pre-ganglionic 
  - Muscarinic $(M_1, M_2, M_3, M_4, M_5)$
  - Nicotinic (Muscle, Neuronal)
  - Post-Ganglionic 
  - Effector Organ 
  - Neurotransmitter

Sympathetic Nervous System

- Neurotransmitters
  - Epinephrine
  - Norepinephrine
- Receptors
  - Adrenergic $(\alpha_1, \alpha_2, \beta_1, \beta_2)$
- Sympathomimetic
  - Adrenergic Agonists
- Sympatholytic
  - Beta blockers

Parasympathetic Nervous System

- Neurotransmitters
  - Acetylcholine
- Receptors
  - Muscarinic $(M_1, M_2, M_3, M_4, M_5)$
  - Nicotinic (muscular, neuronal)
- Parasympathomimetic
  - Cholinergic Agonists
    - Pilocarpine
- Parasympatholytic
  - Most cycloplegics and mydriatics

Autonomic Nervous System

- Parasympathetic Nervous System
  - Tends to have resting effects "rest and digest"
    - But excitatory and inhibitory signals
  - Conserve Energy
  - SLUD
    - Salivation
    - Lacrimation
    - Urination
    - Defecation
  - Pupil constrict
  - Digestion
  - Flushed Skin

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Adrenergic Agents
- **Mydriatics**
  - Phenylephrine – vasoconstrictor
  - Other vasoconstrictor: Naphazoline
  - Cocaine
- **IOP lowering medications (decrease aqueous production)**
  - Beta blockers (timolol)
  - Alpha agonists (brimonidine)
  - Discussed more in glaucoma medications

Cholinergic Agents
- **Miotics**
  - Pilocarpine
  - Carbachol (Miostat) – muscarinic and nicotinic
- **Cycloplegic**
  - Atropine
  - Cyclopentolate
  - Tropicamide
  - Botox (blocks Ach)

Miotics, Mydriatics and Cycloplegics
- **Miotics**
  - Dilate pupil as primary action
  - Nearly always have weaker cycloplegic effect
  - Phenylephrine – no cycloplegic effect
  - Also have α receptors on blood vessels
  - Has effect on skeletal muscle
  - Antimuscaric
- **Cycloplegics**
  - Inhibit accommodation as primary action
  - Nearly always have weaker mydriatic effect
  - Homatropine/Scopolamine
  - Atropine

Miotics, Mydriatics and Cycloplegics
- **Phenylephrine**
  - Also have receptors on blood vessels
  - Has effect on skeletal muscle
  - Raise eyelid
- **Atropine**
  - Strongest of cycloplegics
  - Can have systemic toxicity
  - Nearly always on tests – in reality all systemic toxicity and deaths were on very young or mentally challenged patients
  - Look for redness, hot and dry skin, dry mouth, irregular pulse, hallucinations
  - Be cautious when administering to young children or with mentally challenged patients

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Glaucoma
- IOP lowering medication
- Two ways to lower IOP
  - Increase outflow of aqueous
  - Decrease production of aqueous
- Classified by mechanism of action
  - Beta blockers (yellow)
  - Alpha Agonists (purple)
  - Prostaglandin Analogues (teal)
  - Carbonic Anhydrase Inhibitors (Orange)
  - Combination (blue)

IOP Lowering Medications
- Beta blockers
  - Non-selective for beta receptors
    - Beta 1 on ciliary body
    - Beta 2 on heart, lungs
  - Contraindicated in lung problems (asthma) or heart
    (low pulse or blood pressure)
  - Timolol 0.25%, 0.5% (Timoptic, Timoptic XE,
    Betimol, Istatol)
  - Levobunolol (Betagan)
  - Carteolol (Ocupress)
  - Betoptic S – Beta 1 selective

IOP Lowering Medications
- Adrenergic Receptors
  - Stimulation of beta receptors increases production
  - Stimulation of alpha receptors decrease production
  - Uses Carbonic Anhydrase to actively form aqueous
    (80%)

IOP Lowering Medications
- Cholinergic Agonists
  - Pilocarpine
    - Stimulates muscarinic receptors, stimulating
      accommodation, mechanically pulling open open
      trabecular meshwork
    - Many side effects – accommodation, brow ache
    - Carbchol (MioStat) – intraocular, longer lasting

IOP Lowering Medications
- Adrenergic Agents – affect alpha or beta
  receptors
- Alpha agonists
  - Affect alpha 2 receptors
  - Decrease production and increase outflow
  - Brimonidine 0.2%, 0.15% (Alphagan 0.15%, 0.1&)
    - High allergic reaction rate in higher % concentrations
  - Lopidine

IOP Lowering Medications
- Carbonic Anhydrase Inhibitors
  - Oral and Topical
  - Inhibit carbonic anhydrase, reducing production
    - 80% of aqueous production is actively produced and
      requires anhydrase
  - Topical
    - Brinzolamide (Azopt)
    - Dorzolamide (Trusopt)
  - Oral
    - Acetazolamide (Diamox), Methazolamide (Neptazane)
  - Contraindicated with sulfa allergies
  - Oral side effects (tingling, fatigue, metallic taste,
    kidney stones)
IOP Lowering Medications
- Prostaglandin analogues
  - Latanoprost (Xalatan)
  - Lumigan
  - Travatan
  - Mimic Prostaglandins
  - Increase uveoscleral outflow
  - Prostaglandins are naturally occurring inflammatory markers, however concentration is low so there is no evidence to support causing inflammation in eye
  - Known side effects of skin pigmentation, increase iris pigmentation, lash growth (Latisse)

Inflammatory Process
- When there is an insult to the body it responds with inflammation
  - Beneficial to prevent infection and start healing
  - Some effects need to be tempered or eliminated
- Acute and chronic inflammation
- Main signs of inflammation:
  - Heat - vasodilation
  - Redness - vasodilation
  - Pain – chemicals stimulate nerve endings
  - Swelling – increased vascular permeability
  - Loss of Function – many reasons

IOP Lowering Medications
- Combo
  - Combigan (brimonidine and timolol)
  - Cosopt (timolol and dorzolamide)
  - Simbrinza (brinzolamide and brimonidine)

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Corticosteroids

- Control inflammation, in various parts of body and eye
- Systemic and topical steroids
- Commonly in eye these are
  - Conjunctiva – scleritis, episcleritis
  - Cornea – edema, burns, haze, rejection (grafts)
  - Uveitis
  - Optic Nerve – any inflammation (neuritis)
  - Retina – edema, inflammatory syndromes
- Reduce redness, pain, swelling
  - Also decrease allergic response (histamines, mast cells)
- Very non-specific and acts high up in pathway

Topical Steroids

- Difluprednate 0.05% (Durezol)
  - Emulsification greatest physiologic effect
- Prednisolone Acetate 1% (Pred Forte, Omnipred)
  - Acetate, good penetration, what most others are compared to
- Prednisolone Acetate 0.12% (Pred Mild)
  - Pred Mild
- Dexamethasone 0.1%
  - Sodium phosphate (Decadron) and suspension (Maxidex)
- Loteprednol 0.5% (Lotemax)
- Loteprednol 0.2% (Alrex)
- Fluoromethalone 0.1% (FML)
- Also many combination Antibiotic/Steroids – will be covered in Antibiotic Section

Injectable Steroids

- Multiple advantages
  - Can be put nearer to location
  - Depot deposited (longer lasting)
  - Can have greater penetration (intravitreal)
- Side effects correlate with some of those advantages, though
- Commonly include
  - Triamcinolone (Kenalog)
  - Decadron
  - Ozurdex*
- Multiple areas
  - Subconjunctival
  - Sub-tenon’s
  - Intravitreal
  - Translesional/Subdermal

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NSAIDs
- Non-Steroidal Anti-Inflammatory Drugs
  - Work lower down inflammatory pathway
  - Less effective in reducing inflammation, but fewer side effects
  - Decrease inflammation and fever, as well as pain (analgesic)

Ocular and systemic side effects of NSAIDs – ocular from drops, systemic from oral
- Ocular
  - Corneal melt
  - Corneal toxicity
- Systemic
  - GI upset and ulcers
  - Renal dysfunction
  - Photophobia

Special notes
- Aspirin is non-reversible, has anticoagulating properties (81mg “baby aspirin”)
- Can combine ibuprofen with acetaminophen for much better pain control without overdosing
  - August 2013 reports 500mg acetaminophen and 200mg ibuprofen exceeds pain control of Vicodin (hydrocodone and acetaminophen) or other combination opioids/NSAIDs

Ocular use approved for:
- Reducing post-operative inflammation
- Reducing risk of post-operative CME
- Can treat CME (if mild, often started first due to being non-invasive)
- Allergic conjunctivitis

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**Allergic Cascade**
- Cascade of events that causes allergic response
- Allergic response wide range of symptoms from mild to severe, usually includes itching, redness, swelling, or anaphylactic
- Allergen (environmental stimulus) binds to IgE that is attached to a mast cell, which then releases histamine
- Histamine interacts with histamine receptors, majority of symptoms from binding H1 receptor

**Anti-Allergy Medications**
- Oral antihistamine
  - Benadryl (first generation)
    - Crosses blood brain barrier
  - Claritin, Allegra, Zyrtec
    - All anticholinergic (parasympathetic system)
      - Increase dry eye
- Topical
  - Bepotastine besilate (Bepreve)
  - Alcaftadine (Lastacaft)
  - Olapatadine (Pataday, Patanol)
  - Ketotifen fumarate (Zaditor) - OTC

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**Infections**
- Infection occurs when a microorganism invades the body, and the body can't repel it
- Can be bacterial, fungal, viral, or parasitic
- Immune system divided into two systems
  - Innate – mechanical barriers and non-specific cells
  - Adaptive – responds following exposure
- Immune compromised (HIV/AIDS, on steroids etc) are more susceptible
- Nearly always has associated inflammation, but inflammation and infection are NOT the same
Anti-Infective Agents

- Each type of anti-infective is designed to combat a certain type of infection
  - Antibacterial (bacteriostatic and bacteriocida) – bacteria
  - Antiviral – virus
  - Antifungal – fungal
  - Antiparasitic – parasite

- “Spectrums of action” for each drug – the range of microbes the drug is effective against

Antibacterial Agents

- Macrolides – inhibit protein synthesis G+>>G-
  - Erythromycin, azithromycin, clarithromycin
- Sulfonamides – disrupt folate synthesis G+>>G-
  - Bacteriostatic
  - Bactrim, AK-Sulf
- Fluoroquinolones – prevent DNA duplication
  - 1st to 4th generation
  - Good G+, with increasing generation increases G-
  - Ciprofloxacin (Ciloxan), ofloxacin (Ocuflax), moxifloxacin (Vigamox), gatifloxacin (Zymar, Zymaxid), levofloxacin (Levaquin), besifloxacin (Besivance)

Antiviral Agents

- Effective against viruses
- Mostly used to treat Herpes Simplex and Varicella Zoster, as well as cytomegalovirus
- Herpes Simplex
  - Type I and Type II – usually Type I (cold sore)
  - Varicella Zoster – chicken pox, follows trigeminal nerve
  - Hutchinson’s Sign
  - Zoster vaccine

Antibacterial Agents

- Combat bacterial infections
- Classified into two categories
  - Bacteriostatic – Prevent further bacterial growth
  - Bacteriocidal – Kills bacteria
- Large spectrum of bacteria, no one drug that kills all
- Biggest difference in range is based on cell wall of bacteria
  - Gram Positive – Staphylococcus and Streptococcus
    - Has thick cell wall
  - Gram Negative – pseudomonas, haemophilis
- Resistance – as antibiotics are used, bacteria can develop resistance to them, making that antibiotic less useful

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Antibacterial Agents

- Most antibacterials will have GI upset as side effect due to disrupting normal flora within GI tract
- There are true allergic reactions (redness, itching, rash, problem breathing etc)
- Allergic Reactions
  - Most commonly to penicillin or cephalosporin
  - 20% cross reactivity, so if allergic to one, considered allergic to both
  - Also sulfonamides
- Reactions can be fatal
- Stevens-Johnson Syndrome
  - Severe allergic reaction** - life threatening where epidermis separates from dermis – emergency, treated in burn ward
  - Black box warning for fluoroquinolones – tendinitis and rupture
  - Tetracyclines – bone growth, tooth decolouration, tinnitus, photosensitivity of skin

Antibacterial Agents

- Penicillins – inhibit cell wall production (G+)
  - Penicillin V, Amoxicillin
- Cephalosporins – inhibit cell wall production (G+)
  - Keflex, Aneef
- Aminoglycosides – inhibit protein synthesis (G+>>G+)
  - Tobramycin, gentamycin, neomycin
- Tetracyclines (G-, G+)^
  - Tetracycline, doxycycline, minocycline
  - Can have many side effects – inhibit bone growth and permanent teeth discoulouration in children, photosensitivity of skin in adults, SJS, and tinnitus all common

Antiviral Agents

- Effective against viruses
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- Herpes Simplex
  - Type I and Type II – usually Type I (cold sore)
- Varicella Zoster – chicken pox, follows trigeminal nerve
  - Hutchinson’s Sign
  - Zoster vaccine
Antiviral Agents

- Oral and Topical
  - Topical
    - Gangclovir gel (Zirgan)
    - Trifluridine (Viroptic)
  - Oral
    - Valacyclovir (Valtrex)
    - Acyclovir

- Often injected:
  - Foscarnet
  - Ganciclovir
  - Usually for CMV in patients with AIDS/HIV

Antifungal Agents

- Fungal infections tend to be slow growing but can be very damaging with often poor prognosis

- Two main types of fungal infections
  - Filamentary – Most commonly Aspergillus, sometimes Fusarium
  - Yeast – Most commonly Candida

- Only one drug (natamycin) designed for topical available in US, others adapted for ocular treatment:
  - Natamycin – best for filamentary
  - Fluconazole – best for yeast
  - Amphotericin B – very toxic to cornea, but often needed

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Systemic Effects of Ocular Medications

- Effects of ocular medications all can have systemic effects, though often much reduced

- Can reduce side effects by punctal occlusion when instilling

- Some common things to watch for:
  - Beta blockers – can affect vasoconstriction and pulse, watch for breathing or cardiac problems
  - CAIs – metallic taste
  - Phenylephrine – could increase heart rate, contraindicated in pregnant patients
  - Atropine – anticholinergic - possible parasympatholytic crisis
  - Any drug (often sulfa or antibiotics) – SJS

Ocular Effects of Systemic Medications

- Prednisone – PSC, increase IOP
- Alpha blockers (Flomax) – IFIS and poor iris dilation
- Antihistamines – Dry Eye
- Amiodarone – vortex keratopathy
- Chloroquine, Hydroxychloroquine (Plaquenil) – maculopathy, rare vortex keratopathy
- Oral contraceptives and tetracyclines – papilledema
- Ethambutol – optic neuritis
- Barbituates – optic atrophy

Combination Anti-Bacterial/Steroid

- Combination drops that include anti-bacterial and steroids
  - Tobradex – tobramycin and dexamethasone
    - This is NOT Tobrex
  - Maxitrol – neomycin, polymixin B, dexamethasone
    - Higher allergy rate (neomycin)
  - Zylet – loteprednol and tobramycin

- Extremely common prescribed
- Difference in stopping steroid vs antibacterial
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The primary neurotransmitter of the parasympathetic nervous system is:

- A) Acetylcholine (Ach)
- B) Epinephrine/Norepinephrine (Epi/Norepi)
- C) Dopamine
- D) GABA

Which of the following situations should cause you concern?

- A) Instilling tropicamide in a pregnant patient
- B) Instilling a steroid in a patient who just finished a course of Zirgan and Valtrex for herpes simplex
- C) Instilling Atropine in a child with Down's Syndrome
- D) Instilling a prostaglandin in a patient with sulfa allergies

Phenylephrine works as a __________ system, while most cycloplegics work as ____________

- A) sympatholytic, sympathomimetic
- B) sympathomimetic, parasympatholytic
- C) sympathomimetic, parasympathomimetic
- D) parasympatholytic, sympathomimetic

The ________ and ________ of the autonomic nervous system work together to balance each other

- A) Parasympathetic, Antiparasymathetic
- B) Sympathetic, antisymathetic
- C) Sympathomimetic, Parasymathometric
- D) Parasympathetic, Sympathetic

Match the cap colour with the drug class

- Diating agents
- Miotics
- Antibiotics
- NSAIDs
- Steroids
- Beta blockers
- Alpha agonists
- CAIs

- Pink/White
- Tan
- Orange
- Grey
- Red
- Purple
- Green
- Yellow
Punctal occlusion does when instilling drops?
- A) Reduces risk of contamination
- B) Reduces risk of systemic adverse events
- C) Increases potency of drop
- D) Increases effective concentration of drop

Steroids should be used in which of the following situations?
- A) Fungal infection
- B) Viral infection
- C) Inflammation
- D) Allergic reactions
- E) A and B
- F) C and D

Systemic steroids can cause which of the following?
- A) Cataracts
- B) IOP increase
- C) Blood sugar dysfunction
- D) All of the above

Which of the following IOP lowering medications work on the adrenergic receptors or the sympathetic nervous system – choose all that apply?
- A) CAIs
- B) Beta blockers
- C) Prostaglandin analogues
- D) Alpha agonists

Which of the following could be contraindications for Cosopt (Timolol-Dorzolamide)?
- A) Breathing problems
- B) Low pulse
- C) Sulfa allergy
- D) All of the above

Which is broader acting in its effects on the body?
- A) Corticosteroids
- B) Reversible NSAIDs
- C) Irreversible NSAIDs
- D) Antihistamines
What two medications could be combined without increasing the risk of overdosing?
- A) Aspirin and Ibuprofen
- B) Ibuprofen and Naproxen
- C) Naproxen and Aspirin
- D) Ibuprofen and Acetaminophen

A topical antiviral is:
- A) Zirgan (ganciclovir)
- B) Natamycin
- C) Tobradex
- D) Prednisolone

Steroids work to inhibit ___________ which is relatively __________ while NSAIDs inhibit __________ which is relatively __________
- A) COX (cyclooxegenase), upstream, Phospholipase, downstream
- B) COX (cyclooxegenase), downstream, Phospholipase, upstream
- C) Phospholipase, upstream, COX (cyclooxegenase), downstream
- D) Phospholipase, downstream, COX (cyclooxegenase), upstream
- E) I stopped reading already

If you have seasonal ocular allergies the best choice to minimize symptoms would be:
- A) Start antihistamine 2 weeks before the onset
- B) Start mast cell stabilizers/antihistamine combo 2 weeks before onset
- C) Take a antihistamine/mast cell stabilizer at first symptoms
- D) Start antihistamine at first symptoms

The drop with the largest spectrum of action (coverage) is:
- A) 1st generation fluoroquinolone
- B) tobramycin
- C) 3rd generation fluoroquinolone
- D) erythromycin

The most severe adverse reaction listed is:
- A) Conjunctival injection
- B) Epiphora
- C) Swelling of mucosal membranes
- D) Blurriness instantly upon instillation
Which of the following has a black box warning for tendonitis?

- A) Cephalosporins
- B) Macrolides
- C) Aminoglycosides
- D) Fluoroquinolones

Which of the following situations should cause you concern?

- A) Instilling tropicamide in a pregnant patient
- B) Instilling a steroid in a patient who just finished a course of Zirgan and Valtrex for herpes simplex
- C) Instilling Atropine in a child with Down’s Syndrome
- D) Instilling a prostaglandin in a patient with sulfa allergies

If a patient is allergic to penicillin, what are they immediately also considered allergic to?

- A) Cephalosporins
- B) Fluoroquinolones
- C) Macrolides
- D) Aminoglycosides