Ocular Pharmacology: A Conglomeration of New Ideas, New Uses, Old Drugs, & Old Topics

Christopher Borgman, OD, FAAO
Brimonidine (Alphagan-P)

- A highly specific \( \alpha \)-2 adrenergic receptor agonist
- \( \alpha \)-2 receptors at pre-synaptic nerve terminals
- Binding sites for brimonidine localized on the iris
- Activation of \( \alpha \)-2 receptors inhibits the release of the neurotransmitter, norepinephrine
- Therefore, norepinephrine is not available for receptor activation & adrenergic Pupil Dilation
  - Decreased by 1-2 mm
- Onset 30 mins; up to 4-6 hrs

The Scotopic Miosis

- Speculated to be:
  - Due a change in balance between the pupil sphincter and pupil dilator muscles.
  - Tonus of the cholinergic driven sphincter remains intact (PNS)
  - Dilator (SNS controlled) is relaxed in the presence of the \( \alpha \)-2 agonist
  - Therefore, the sphincter has increased control over pupil size
    - the balance has shifted to PNS ➔ Smaller pupil
Why less effect on pupil size in bright illumination?

- Brimonidine
  - Has no effect on cholinergic driven sphincter muscle in photopic conditions (PNS)
  - There is a less obvious size difference with and without brimonidine

- Therefore, photopic pupil size is relatively normal

Brimonidine

<table>
<thead>
<tr>
<th>Effect</th>
<th>Brimonidine</th>
<th>Pilocarpine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ciliary spasm</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Effective in Photopic?</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Effective in Scotopic?</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Systemic side effects?</td>
<td>Limited</td>
<td>SLUDGE</td>
</tr>
<tr>
<td>Ocular side effects?</td>
<td>Allergy</td>
<td>RD</td>
</tr>
</tbody>
</table>

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Alphagan (Brimonidine) & Redness Reliever

Brimonidine tartrate 0.025%

- Diluted brimonidine solution → vasoconstriction
- Darkens pigmentation
- Just coupled Phase 3 trials (Bausch & Lomb)
- No rebound hyperemia with discontinuation
- No tachyphylaxis noted
- Onset within 5 minutes
- Serum is work on smaller caliber conjunctival vessels without affecting larger vessels so blood flow is not affected
- Duration of effect ~ 4 hrs

Wouldn't Pilocarpine work too?

- Brimonidine
- Pilocarpine

Bottom Line: consider Brimonidine in patients with scotopic vision complaints
Brimonidine Rosacea Gel

- Approved for rosacea redness/erythema
- Dosing: Apply to erythematous patches once daily
- MOA: post-synaptic alpha agonist → sympathomimetic
- Causes vasoconstriction of facial blood vessels
- Onset: 30 minutes; Duration: 12 hours
- FDA category B
- Main SE’s:
  - *Flushing/redness (8-10%)
  - Worsening of rosacea (5%)
- 1 month study showed modest results only:
  - 28% saw reduction in redness with brimonidine
  - 10% saw reduction in redness with vehicle
- Other use: Immature scar redness reducer

PTC / IIH Treatment Option:

1. Weight loss (5-10% is sometimes curative)
2. Carbonic anhydrase inhibitors
   - Acetazolamide (Diamox)
   - No oral steroids → weight gain
3. Ventriculoperitoneal Shunt / Lumboperitoneal Shunt
   - Headaches only; vision stable
4. Optic Nerve Penetration
   - Vision/Visual Field worsening; no headaches
5. Venous Sinus Stenting
   - In venous sinus stenosis

Topiramate (Topamax)

- MOA:
  - Post-synaptic alpha agonist
  - Sympathomimetic activity
  - Causes vasoconstriction of facial blood vessels

Topamax vs. Diamox?

- Acetazolamide: CAI inhibitor: works on diencephalon and extracellular spaces
- Topiramate: CAI, works on diencephalon and extracellular spaces
- Both inhibit glutamate reuptake
- Topiramate causes CNS side effects

Topiramate Ocular Side Effects

- **Angle closure glaucoma and myopic shift!!!**
- Risk: 5% of those without 2 weeks of therapy
- MOA: decreases IOP by decreasing aqueous humor production
- Hypothalamus-mediated decreases in sodium, reducing cerebral metabolism
- Not related to dosage; not pattern-dependent
- Idiopathic response... no pattern

<table>
<thead>
<tr>
<th>Dosage (mg/day)</th>
<th>Incidence of Angle Closure/Myopia</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;50</td>
<td>4%</td>
</tr>
<tr>
<td>50-75</td>
<td>33%</td>
</tr>
<tr>
<td>100</td>
<td>13%</td>
</tr>
<tr>
<td>&gt;100</td>
<td>7%</td>
</tr>
</tbody>
</table>

Topiramate MOA:

- All salts increase IOP & acute angle closure by increasing ciliary muscle tone of the iris → HTN is usually followed by ptosis
- BHT
- Thiazide diuretics
- Acetazolamide
- Ciliary body damage is a final common pathway
- Ciliary processes release tramadol, causing increased production of anterior chamber angle
- Relocation of the lens fiber causes less thickening → increased myopia
Topiramate-induced angle closure glaucoma???

Check list...
- Seeks medication list
- "Has the medication started? Increased dosage recently?"
- Myopic shift?
- Narrow anterior chamber at MLA?
- Elevated IOP?
- Dilation of ciliary vessels/edema?
  - 2-4 mm with mydriasis
  - Scleral indentation
- Biometry?
  - Contact with prescribing physician for...
- Reduce IOP, cycloplegia patient
  - Ion channel blocker

Rechallenge with Topiramate???
- Controversial results...
- Pronostaet al. → 3 cases... ( recurance upon rechallenge
- Gubady SS → recurrence upon rechallenge with lower dosage 5 days later
- Jurgens TP et al. → 1 case... ( recurance with rechallenge

Topiramate and EtOH-ism???
- MOA: suppression of ethanol-induced norepinephrine
  - Dopaminergic stimulation
  - Inhibition of EtOH-induced effects

"...there is now solid clinical evidence to support the efficacy of topiramate for the treatment of alcohol dependence. Topiramate's therapeutic effects appear to be robust with a moderate effect size, thereby potentially ushering in a new era of a reliably efficacious medicine for the treatment of alcohol dependence."
- Johnson BA, et al. 2010

Abilify & Blurry Vision?

Aripiprazole (Abilify)

- Atypical antipsychotic medication
  - Schizophrenia
  - Schizoaffective disorder
  - Bipolar disorder
  - OCD
  - MANI
- Dopamine receptors (D2 & D3) → partial agonist
- Serotonin receptors (1A) → partial agonist
- Serotonin receptors (5HT) → antagonist

Blurred Vision?

- 3 of 926 subjects (0.37%) cases
- Transient increase lonyeplia

- How?
  - The various mechanisms of drug-induced myopia reported in literature are:
    - accommodation spasm
    - ciliary spasm
    - increase in thickness of stroma and peripheral corneal thickness
    - ciliary body edema and some flooding in forward movement of iris lens diaphragm
    - acute myopia
**Borgmar's Theoretical MOA???

- Studies show:
  - Increased levels of serotonin → increased sympathetic innervation → myokymia!
  - SSRI's and/or MAOI's
- Ability (ziprasidone) is a serotonin receptor blocker (5-HT2A receptor)
- Decreased levels of serotonin → decreased sympathetic innervation → miosis & accomom
- Increased myopia!

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**Topical Timolol & Superior Oblique Myokymia**

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**Dx = Superior Oblique Myokymia**

- First reported in 1906 by Duane "unilateral rotary nystagmus"
- In 1970, Hoyt coined term "superior oblique myokymia"

- Def: monocular quivering/flashing of superior oblique
- Ex: spontaneous monocular diplopia, quivering/jumping of vision, monocular oscillopsia, key is monocular nature
- Oc: low amplitude, high frequency, onset of affected eye intermittent/cyclical frequency, worse when looking down and in towards nose
- Most attacks last between 3-15 sec, rare cases of indefinite attacks

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**SOM Tx Options**

- Observation
- Medical
  - Oral medications
- Surgical
  - EOM/Strab surgery
  - Microvascular decompression

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**New Tx? Topical Beta-blockers??**

- Blyby et al. (1994) showed one case report of a patient's SOM sx being relieved with beta-blockol glaucoma drops
- Based off of case reports which used oral propranolol
- Weak membrane stabilizing abilities of beta blockers ≠ MOA
- MOA: hypothesized that enough drug was absorbed systemically through conjunctival blood vessels to elicit its effect (systemic theory)

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**30 YO WF with SOM x 10 yrs**

- Started topical timolol 0.5% drops BID OD!
- Patient reported 100% resolution of sx after only 2 days of use!!!!
- Phone call 4 months later, still 100% resolution of sx but only using drops QAM OD
- 12+ month later...still sx-free on drops!
Story doesn't end here...

• Given that numbers of SOM are low to begin with......cases of typical beta-blockers providing even better response.
• Bibby et al......hypothesized “systemic theory”
• I developed my own theory......
• Chris Borgman's “Localized Theory”

CB's “Localized Theory”

• In SOM, when successfully treated with topical beta-blockers, the effect occurs locally at the trochlear nerve endings themselves and/or on the trochlear muscle itself, not systemically absorbed via the conjunctival blood vessels.
• I would argue AGAINST Bibby's systemic absorption theory.

Proof of Localized Theory

• After successful Tx for 2+ months...
  • Patient instructed to stop all drops
  • Sx returned to pre-treatment severity in 2-3 days
  • Patient instructed to instill drops in contralateral eye
  • No effect, Sx still remained
  • Patient told to re-start drops in original/affected eye
  • Sx disappeared in 1-2 days of use again
  • No recurrences since

What does this mean?

• Keep in mind.....this is only 1 case.
• Beta-blockers work locally on the ocular tissues themselves
  • Likely on superior oblique muscle itself or the trochlear nerve endings
  • Perhaps not on a systemic level like Bibby et al. hypothesized...
  • “Localized theory” holds water!
  • However, still unproven...needs more research

Interesting Potential Off-Label Uses of β-Blockers???

1. Superior Oblique Myokymia


2. Eyelid Myokymia

MOA: Stabilization of membrane excitability/resting state of action potential (phase 4)

Mineralcorticoid Receptor Antagonists & CSR
Central Serous Chorioretinopathy

- Circumcentered serous RD; usually macular region
- Pathophysiology: unknown
- MAF (48% of cases) 20-50 YO age range normally
- Bilateral: 40%
- Most acute episodes resolve in 3-6 months on own
- Recurrences common (up to 50%) chronic CSCR in 5-10% of cases
- Chronic CSCR = >6-8 mo duration not remission
- Histologically, serous detachment; no exudative CSCR, unknown ME
- Etiology: endogenous cortisol,ushing episodes, psychological stress, Type A personality = risk factors
- Retin, HPV, collagen vascular diseases, W-Fibrosis infection
- PDE, ret-NED, CA's, beta-blockers have been tried with variable success

OCT Evidence of MOA?

- New evidence: diffuse choroidal thickening in CSCR eyes (and contralateral eye)
- **Choroidal vascular hyperpermeability**!

- How does this hyperpermeability occur?
- Unknown still...
- Choroidal vasoconstriction

Corticosteroids

- Produced by adrenal cortex:
  1. **Mineralocorticoids** = aldosterone
     - bind to both mineralocorticoid (MR) and glucocorticoid receptors (GR)
  2. **Glucocorticoids** = cortisol
     - bind to both mineralocorticoid and glucocorticoid receptors too!

- Cross binding to each receptor! Equal affinity for both!
- MDA: Excess cortisol spills over to activate MR receptors as well
- Choroid has both MR and GR; retinas does not!
- Glucocorticoids & Mineralocorticoids both induce choroidal vasoconstriction/thickening and cause vessel dilation and leakage which can overcome RPE's defense -> neurosensory detachment

Mineralocorticoid Receptor

- **MR agonists** -> upregulate KCa2.3 channels -> choroidal vasodilation/leakage -> SRF accumulation
- **MR antagonists** -> down-regulate KCa2.3 channels -> choroidal vasoconstriction -> SRF reduction

- Remember, MR is NOT found in retinal tissues, therefore retina is unaffected by both mineralocorticoids and glucocorticoids

Eplerenone (Inspira)

- FDA-approved in 2003 for HTN; 2005 for CHF
- Oral mineralocorticoid/aldosterone receptor antagonist
  - Competitive antagonist with high selectivity of MR; potassium sparing diuretic
  - Reverses "endothelial vasodilatory potassium channel (KCa,2.3)" activation in choroid
  - Stops/reverses choroidal thickening/leakage; down regulates KCa2.3
  - KCa2.3 only is expressed in choroid, not retina!
  - This is why MRA antagonists do not induce renal vessel vasodilation!
  - Side effects: hyperkalemia
  - Contraindications: liver or renal disease, pregnancy
  - Standard dose for CSCR: 25 mg/day PO x 1 week, then 50 mg/day x 3 months

Eplerenone vs. Spironolactone

- Both are mineralocorticoid receptor blockers!
- Both are potassium-sparing diuretics
  - Risk of hyperkalemia
  - Eplerenone has 10-fold lower affinity for MR than spironolactone
- However, eplerenone has a much higher specificity for MR without antagonizing SRF's

- Eplerenone is best choice with the least probably SRF's at this time between the two.
What is cheapest way to maximum meds for glaucoma with the least amount of drops???

- Latanoprost  → $14.88
- Timolol 0.5%  → $4.00
- Betaxolol 0.2%  → $9.90

What is cheapest way to maximum meds for glaucoma with the least amount of drops???

- Latanoprost  → $14.88
- Dorzolamide/Timolol (2%/0.5%)  → $23.3
What is the cheapest option for steroid and antibiotic combo?

- Pred-G (brand) → $126.51
- Tobramycin/Dexamethasone → $55.54
- Tobramycin/Lopinavir (Cyber) → $222.28
- Neomycin/Polyoxymycin/Dexamethasone → $4.00

$4 List of Generics Available

<table>
<thead>
<tr>
<th>Antihistamine</th>
<th>NSAID's</th>
<th>ABR</th>
<th>Antiviral</th>
<th>Steroids</th>
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<tbody>
<tr>
<td>Loratadine</td>
<td>Naproxen</td>
<td>Azithromycin</td>
<td>Acyclovir</td>
<td>Prednisone</td>
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<tr>
<td>Indomethacin</td>
<td>Amoxicillin</td>
<td>Cefuroxim</td>
<td>Dexamethasone</td>
<td></td>
</tr>
<tr>
<td>Naproxen</td>
<td>Ciprofloxacin</td>
<td>Dexamethasone</td>
<td></td>
<td></td>
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<tr>
<td>M ethosicin</td>
<td>SMZ/TMP</td>
<td></td>
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</table>

Additional Resource for Cheap Meds:
Borgman C.J. Many common conditions respond to inexpensive treatment options. Primary Care Optometry News, January 2015.

Phenylephrine Review...

- Developed in 1933 from EPI
- Potent vasoconstrictor → alpha-1 agonist
- No beta receptor activity at all
- Dilation of pupil without cycloplegia
- Negligible effect on IOP
- Maximum dilation = 15-90 minutes
- Maximum duration of action = 6-7 hrs
- Peripheral vasoconstriction can lead to rapidly elevated SBP in some patients
- Systolic and diastolic are affected

Is the fear justified???

Phenylephrine-Induced HTN

- Widespread use; actual risk is likely lower than reported
- Likely idiosyncratic responses
- Majority of cases are within 10-30 minutes of instillation
- HTN effect is transient; 30-60 minutes duration
- HTN effects coincide with peak tissue and plasma levels
- 2.5% PHE = 10% PHE with dilation
- Ocular hypertension: yes at highest risk
- Determinate hypertension?

- Sinus tachycardia
- Chest pain
- Palpitations
- Perfusion
- Nausea/vomiting
- SOB
- Reflex bradycardia/hypotension

End-Organ Damage
- SAH
- Aneurysm rupture
- Papilledema
- Pulmonary edema
- MI
- CVB
Worst Cases Reported In Literature...

- Cotton pledge soaked in 10% PHE and left on surgical eye
- More than one drop of 10% PHE
- PHE used in conjunction with Atropine
- Multiple rounds of PHE in peds/children

<table>
<thead>
<tr>
<th></th>
<th>Total (n)</th>
<th>10% PHE Severe</th>
<th>10% PHE Increased BP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults</td>
<td>1984</td>
<td>7.56% (n=144/1984)</td>
<td>14.70% (n=274/1984)</td>
</tr>
<tr>
<td>Pediatrics</td>
<td>44</td>
<td>11.36% (n=5/44)</td>
<td>84.09% (n=37/44)</td>
</tr>
</tbody>
</table>

Note: numbers based on 50+ articles on HTN & PHE risk

What about # of drops and risk in **ADULTS**??

<table>
<thead>
<tr>
<th></th>
<th>Total (n)</th>
<th>Risk of causing increased blood pressure in adult patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>10% PHE --- 1 gtt OU</td>
<td>460</td>
<td>2.17% (n=10/460)</td>
</tr>
<tr>
<td>10% PHE --- 2 gtts OU</td>
<td>181</td>
<td>11.05% (n=20/181)</td>
</tr>
<tr>
<td>10% PHE --- 3+ gtts OU</td>
<td>761</td>
<td>26.81% (n=204/761)</td>
</tr>
<tr>
<td>2.5% PHE --- 1 gtt OU</td>
<td>767</td>
<td>0.65% (n=5/767)</td>
</tr>
<tr>
<td>2.5% PHE --- 2 gtts OU</td>
<td>814</td>
<td>1.93% (n=8/814)</td>
</tr>
</tbody>
</table>

What about # of drops and risk in **PEDS**??

<table>
<thead>
<tr>
<th></th>
<th>Total (n)</th>
<th>Risk of causing increased blood pressure in pediatric patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>10% PHE --- 1 gtt OU</td>
<td>4</td>
<td>100% (n=4/4)</td>
</tr>
<tr>
<td>10% PHE --- 2 gtts OU</td>
<td>20</td>
<td>100% (n=20/20)</td>
</tr>
<tr>
<td>10% PHE --- 3+ gtts OU</td>
<td>20</td>
<td>65% (n=13/20)</td>
</tr>
<tr>
<td>2.5% PHE --- 1 gtt OU</td>
<td>31</td>
<td>0% (n=0/31)</td>
</tr>
<tr>
<td>2.5% PHE --- 2 gtts OU</td>
<td>0</td>
<td>Unable to quantify with available studies</td>
</tr>
<tr>
<td>2.5% PHE --- 3+gtts OU</td>
<td>211</td>
<td>7.11% (n=15/211)</td>
</tr>
</tbody>
</table>

PHE Guidelines

- One drop of 2.5% PHE OU should be used without hesitation
- <1% risk of elevated BP with one round of 2.5%
- 5-10% PHE is best reserved for stubborn posterior synechiae cases
- If used, no more than one drop in each eye, or two drops total in single eye
- Do NOT use 5-10% in infants
- Only use one drop of 2.5% PHE OU in select cases in pediatrics

Borgman's Rule: no more than 2 rounds of 2.5% PHE OU should be used in any one visit in adults regardless of BP

Cardiovascular Adverse Effects of Phenylephrine Eyedrops
A Systematic Review and Meta-analysis

- Conclusion: Phenylephrine, 2.5% leads to no clinically relevant change in BP or HR and can be considered safe to use in clinical routine. The changes in BP and HR seen with phenylephrine, 10% are short lived and of uncertain clinical relevance.
So...is the ear justified??

Ethambutol Ocular Toxicity Risk Calculations

Ethambutol
- Antituberculous medication; predominantly bacteriostatic
- Treatment: minimum of 6 months in most cases
- Drug most often implicated in optic neuropathy
  - D-isoamide = compartment form
  - L-isoamide = toxic form

- Loading dose initially 25 mg/kg/day x 2
- Maintenance dose = 15-20 mg/kg/day
- Initial dose = 15 mg/kg/day
- >25 mg/kg/day = High dose
- No null dose of EMB has been reported!

Table 1: Percentage risk range and mean risk of developing ocular toxicity based on daily dosing of Ethambutol in regards to milligrams per kilogram per day (mg/kg/day) based on available literature

<table>
<thead>
<tr>
<th>Daily Dose</th>
<th>15 mg/kg/day</th>
<th>17.5 mg/kg/day</th>
<th>20 mg/kg/day</th>
<th>25 mg/kg/day</th>
<th>30-35 mg/kg/day</th>
<th>40-50 mg/kg/day</th>
<th>60-100 mg/kg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk Range</td>
<td>0.62-2%</td>
<td>1.5%</td>
<td>3.6-7%</td>
<td>7.2-9.4%</td>
<td>15.6-18.6%</td>
<td>15-33.3%</td>
<td>40-50%</td>
</tr>
<tr>
<td>Mean Risk</td>
<td>1.31%</td>
<td>1.5%</td>
<td>4.65%</td>
<td>5.8%</td>
<td>16.8%</td>
<td>24.15%</td>
<td>45%</td>
</tr>
</tbody>
</table>
Mean Risk of Ethambutol Optic Nerve Toxicity

Example #1

- A 150 lbs male who is taking 1000 mg Ethambutol daily for his Mycobacterium avium complex infection. What is the total dose per day that the patient is getting and respectively what would be his risk of developing ocular toxicity based on this dose?
  - 150 lbs / 2.2 kg = 68.18 kg of body weight
  - 1000 mg x \( \frac{1}{68.18 \text{ kg}} \) = 15 mg/kg/day
  - ~1.31% risk

Example #2:

- Example #2: A 100 lbs female who is taking 1600 mg Ethambutol daily for her Mycobacterium avium complex infection. What is the total dose per day that the patient is getting and respectively what would be her risk of developing ocular toxicity at this dose?
  - 100 lbs / 2.2 kg = 45.45 kg
  - 1600 mg x \( \frac{1}{45.45 \text{ kg}} \) = 35 mg/kg/day
  - ~16.3% risk

The Calculation

\[
\text{Body Weight (lbs)} \times \frac{2.2 \text{ lbs}}{\text{weight in kilograms}} = \text{dose of mg/kg/day}
\]

\[
\text{Total daily dose (mg)} \times \frac{1}{\text{body weight (kg)}} = \text{dose of mg/kg/day}
\]

Table 1: Percentage risk range and mean risk of developing ocular toxicity based on daily dosing of Ethambutol in regards to milligrams per kilogram per day (mg/kg/day) based on available literature.\(^1,2,4,6-8,12-14,22,24-26,28-30,38-46\)

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<th>Daily Dose</th>
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<td>45%</td>
</tr>
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</table>
Shameless Plug for Article in Review of Cornea & Contact Lenses (2017)

Recommendations...
1. Prior to starting EM3 ➔ Baseline exam
2. 1 month later
3. 3-6 months while on EM3
4. Discontinue with any sign of toxicity
   - Aqueous, Pupil, DFR, HVF, Fundus photos, OCT, color vision at every visit
   - Consider both IOP & J2/304 protocols

- Communicate findings (and risk) to prescribing PCP?

Oral Anticholinergics & Ocular Side Effects

Anticholinergic Medication | Highest Risk of Central Side Effects
---|---
Oxybutynin | High
Propiverine | High
Fesoterodine | Intermediate
Solifenacin | Intermediate
Tolterodine | Intermediate/Low
Darifenacin | Intermediate/Low
Trospium | Low

Oxybutynin
- Parental drug for overactive bladder syndrome
  - 10-17% of the adult population has OBS
- Moderately potent anticholinergic, antispasmodic, and local anesthetic properties
- 19% as potent as trospium in antispasmodic actions
- 4% as potent as trospium in mydriasis
- Blurred vision occurs in 3.8% of patients taking medication

Parasympathetic Nervous System Review
- Parasympathetic innervation control
  - Accommodation
  - Lacrimation
  - Pupil dilation
  - Conjunctiva
  - Vomiting
- M2A: muscarinic receptor agonist with Amytholdine
- M2, M3, M4, and M5 receptors identified
- M3 receptor for pupillary dilation, accommodation, accommodation, binocularity
- Oxybutynin blocks M1R, M3
- M1R
- M1R
- Converge
- Double vision
- Binocular vision extinction

Oxybutynin
- Of all oral anticholinergics, oxybutynin has highest risk of systemic/ocular SE

Why Oxybutynin with highest SE profile?
- In order to cause CNS effects, any anticholinergic drug must first pass through the blood-brain barrier, which is formed by the endothelial cells that line cerebral capillaries and to their continuous tight junctions

<table>
<thead>
<tr>
<th>Oxybutynin</th>
<th>Other OAB medications</th>
</tr>
</thead>
</table>
| Small molecular size | Larger molecular size
| High lipophilicity | Low lipophilicity
| Neutral polarity | High polarity

- Oxybutynin’s properties allow it to pass through the blood-brain barrier much more easily than any of the other related molecules of this same family of drugs
- If M1 receptor antagonism is too severe ➔ Alzheimer’s-like complications possible
Shameless Plug


Ocular Side Effects

- **Ocular Surface Dryness**
  - M3 receptor antagonism on lacrimal gland
- **Decreased Accommodation**
  - ≥1.00 D in 3-7% of patients
  - Within first 4 weeks of initiating therapy
- Binocular Vision Dysfunction
- Pupil mydriasis
  - Usually <1 mm

Antimuscarinic Inhalers:

- Combivent (ipratropium/albuterol)
- Atrovent (ipratropium)
- Spiiva (tiotropium)

Questions???

- Thank you!
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2016 was the C.Y.E.R.