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

Chris Borgman, OD, FAAO

Disclosures:
I have no disclosures to report.

Ground Rules…

- References/sources available upon request
- I’m not perfect…
- Please email me with questions:
  chborgman@sco.edu

Alphagan (Brimonidine) & Pupillary Miosis???

Brimonidine (Alphagan-P)

- A highly specific α-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
- Dilator is relaxed in the presence of the alpha-2 brimonidine
- Therefore, the sphincter has increased control over pupil size
  ➔ the balance has shifted ➔ Smaller pupil
Why the scotopic miosis with brimonidine?

In the sympathetic system:
- Norepinephrine released adrenergic nerve terminals
- Stimulating alpha-1 receptors ->
  - Mydriasis
  - By constriction of the iris dilator

In dim illumination:
- Norepinephrine mediated Dilator Muscle:
  - Cause of pupil dilation
  - Unopposed by the acetylcholine mediated sphincter muscles.

Why less effect on pupil size in bright illumination?

- Brimonidine
  - Has no effect the 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.

Alphagan (Brimonidine) & Redness Reliever

Brimonidine tartrate 0.025%

- Dilated brimonidine solution → vasoconstriction
- Just completed Phase 3 trial (Beach & Lamb)
- No rebound hyperemia with discontinuation
- No tachyphylaxis noted
- Onset within 5 minutes
- Seems to work on smaller caliber conjunctival vessels without affecting larger vessels so blood flow is not affected
- Duration of effect <4 hrs

Brimonidine Rosacea Gel

- Approved for rosacea redness/erythema
- Dosing: Apply to erythematous patches once daily
- MAB: 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 (4-10%)*
  - Worsening of rosacea (5%) 4 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

Topical Timolol & Superior Oblique Myokymia
**Dx = Superior Oblique Myokymia**

- First reported in 1906 by Drane “unilateral rotary nystagmus”
- In 1970, Hoyt coined term “superior oblique myokymia”

- **Def**: monocular quivering/fitting of superior oblique
- **Sx**: spontaneous monocular diplopia, quivering/jumping of vision, monocular oscillopsia, key is monocular nature
- **Sx**: low amplitude, high frequency intontion of affected eye, intermittent/cyclic 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/Steal surgery
  - Microvascular decompression

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

- Bibby et al. (1994) showed one case report of a patient’s SOM Sx being relieved with betaxolol glaucoma drops
- Based off of case reports which used oral propranolol
- Weak membrane stabilizing abilities of beta blockers = MOA

- MOA: hypothesis 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!

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**Story doesn’t end here…**

- Given that numbers of SOM are low to begin with……cases reports of *topical* beta-blockers providing relief of Sx are even rarer

- Bibby et al……hypothesized “systemic theory”

- I developed my own theory……
- Chris Borgman’s “Localized Theory”

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**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 2-3 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 restart 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 acting 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
   - MOA: stabilization of membrane excitability/resting state of action potential (phase 4)

2. Eyelid Myokymia

Mineralcorticoid Receptor Antagonists & CSR

Central Serous Chorioretinopathy

- Chronic/sustained RD
- Pathophysiology: unknown
- M/F (72%-88% of cases), 30-50 YO age range normally
- Bilateral in 40%
- Most acute episodes resolve in 3-6 months on own
- Recurrences common (up to 50%) in chronic CSR, 5-15% of cases
- Chronic CSR >3-4 mo duration in most studies
- Historically, corticosteroids can augment CSR, unknown MOA
- Enlargement/migration correlated, Chediak-Higashi syndrome, psychological stress, Type A, pregnancy, risk factor
- Some: FNI, collagen vascular diseases, HLA type positive
- PDT: anti-VEGF, GC's, beta-blockers have been tried with varied success

OCT Evidence of MOA?

- New evidence: diffuse choroidal thinning in CSR eyes (and contralateral eye)
- Choroidal vascular hyperpermeability

- How does hyperpermeability occur?
- Unknown still
Corticosteroids

- Produced by adrenal cortex
  1. **Mineralcorticoids** α aldosterone
     - Tied to both mineralocorticoid (MR) and glucocorticoid receptor (GR)
     - Glucocorticoid: cortisol
     - First 6 months of glucocorticoid therapy helps avoid mineralocorticoid effect
  1. **Glucocorticoid: cortisol**
     - Cross at both mineralocorticoid and glucocorticoid receptor too

- Cross binding to each receptor: equal affinity for both MR, GR
- MR: excess cortisol spills over to downregulate MR receptors as well
- Glucocorticoids: Mineralcorticoids both induce choroidal edema/thickening and cause vessel dilatation and leakage which can overcome SRF's defenses
  - **Corticosteroid-induced posterior uveitis**
  - **Corticosteroid-induced posterior uveitis**

**Eplerenone (Inspira)**

- FDA-approved in 2002 for HTN; 2003 for CHF
- Oral mineralcorticoid-receptor antagonist (MR)
  - Competitive antagonist with high selectivity for MR: potential safety advantage
  - Reverses edema and sodium/potassium channel (KCC2.3): activation in choroid
  - Stops/delays choroidal thickening/leakage: downregulates KCC2.3
  - KCC2.1 only is upregulated in choroid, not retina
  - That's why MCRI antagonists do not induce retinal vessel dilatation
- 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
- Follow up 1 month, then 3 months; repeat OCT

**Mineralcorticoid Receptor**

- MR agonists: upregulate KCC2.3 channels ε choroidal vasodilation/sequestration ε SRF accumulation
- MR antagonists: down-regulate KCC2.3 channels ε choroidal vasodilation/sequestration ε SRF reduction

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

**Eplerenone vs. Spironolactone**

- Both are mineralocorticoid receptor blockers
- Both are potassium-sparing diuretics
- Both are hypotensives
- Eplerenone has 10-20x lower affinity for MR than spironolactone
- However, eplerenone has a much higher specificity for MR without antagonizing SR's

- Eplerenone is best choice with the least probably SRF's at this time between the two

**How effective is Eplerenone on CSCR?**

- Reduced SRF within 1 month = 25-71%
- Reduced SRF within 3 months = 83%
- Complete resolution within 3 months = 64-67%

- It's a limited adverse effect profile and high selectivity and specificity (to the mineralocorticoid/glucocorticoid receptors) make eplerenone an ideal treatment modality for CSCR.


**Bottom Line..**

- Consider Eplerenone in CSCR lasting >3 months
- 25mg daily x 1 week then 50 mg PO daily for up to 3 months
- Treat edema until resolution of fluid or 3 months of treatment
- Monitor serum potassium levels; co-manage with PCP
- Monitor serum potassium levels monthly
- Discontinue med if:
  - Excessive increase of >5 mmol/l
  - Creatinine increase of >50% initial baseline
  - Likely best avoided in patients with renal problems
- Monitor q4-6 weeks while on medication with OCT's
What is cheapest way to maximum meds for glaucoma with the least amount of drops???

- Latanoprost: $14.88
- Timolol 0.5%: $4.00
- Brimonidine 0.2%: $9.90

TOTAL: $28.78/month

What is cheapest way to maximum meds for glaucoma?

- Latanoprost: $14.88
- Dorzolamide/Timolol (2%/0.5%): $23.53

TOTAL: $38.41/month

What is cheapest way to get separate steroid and antibiotic?

- FML 0.1%: $14.06
- Pred Acetate 1%: $29.63
- Dexamethasone 0.1%: $23.00
- Timolol: $4.00
- Polymyxin/TMP: $4.00

TOTAL: $27.00/month

What is cheapest way to maximum meds for steroid and antibiotic?

- Pred G (brand): $128.51
- Tobramycin/Dexamethasone: $55.54
- Tobramycin/Lomeprazol (Tablet): $210.28
- Neomycin/Polymyxin/Dexamethasone: $4.00

TOTAL: $4.00/month

$4 List of Generics Available

Antihistamine | NSAIDs | Acid | Antibiot | Immune
---|---|---|---|---
Loratadine | Naproxen | Naproxen | Acyclovir | Prednisone
Indomethacin | Acetaminophen | Acetaminophen | Dexamethasone
Ibuprofen | Ciprofloxacin | Ciprofloxacin | Prednisone
Meloxicam | SMZ/TMP | SMZ/TMP | Prednisone

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

Abilify & Blurry Vision?

Aripiprazole (Abilify)

- Atypical antipsychotic medication
- Dopamine receptor (D3 & D2) agonist
- Serotonin receptor (5HT2A) partial agonist
- Serotonin receptor (5HT2C) antagonist

- Schizophrenia
- Affective disorder
- Resistant depression
- Bipolar disorder
- OCD
Blurred Vision?

- 3 of 926 subjects (0.32% cases)
- **Transient increase in myopia**

- How?
  - The various mechanisms of drug-induced myopia reported in literature are:
  - accommodation error
  - ciliary muscle spasm
  - increase in thickness of the lens and peripheral axial diffusion
  - Ciliary body retraction and adhesions resulting in posterior movement of the lens diaphragm

Borgman’s
Theoretical MOA??

- Studies show:
  - Increased levels of serotonin → increased sympathetic innervation → mydriasis
  - SSRI’s and/or MAOI’s
  - Aplify (sarpiprazole) is a serotonin receptor blocker 5-HT2A receptor
  - Decreased levels of serotonin → decreased sympathetic innervation → miosis & accommodation
  - Increased myopia

Pigment Epithelial Derived Factor

**Vs.**

Anti-VEGF

New Horizons in Ocular Neovascularization Tx’s

- Intravitreal VEGF injections
- Topical Anti-VEGF eye drops
- Pigment epithelium-derived factor

Intravitreal anti-VEGF Injections…

- Avastin, Lucentis, Eylea
- Used as monotherapy or in combination therapy
- **MoA:** Bind to free-floating VEGF molecules to prevent attachment to endothelial surface receptors
  - By definition, do nothing for underlying disorder...
  - Have been shown to stimulate regression of neovascularization within 1-2 days
  - Short-half lives (~20 days), wear off over time

New: Pigment epithelium-derived factor (PEDF)

- Patent endothelial, broad-acting angiogenesis inhibitor
- **MoA:** Inhibits formation of VEGF
  - Targets new blood vessels with no measurable effect on mature blood vessels
  - Homeostatic balance between VEGF and PEDF
  - Increased VEGF = Decreased PEDF

**KPE** → **PEDF** → **VEGF** → **VEGF receptors** → Neovascularization
Other effects of PEDF…

- Neuroprotection in CNS
- Eye include: Glaucoma
- Protection from AMD, glaucoma
- Reduces ischemia in retinal tissues
- Inhibits cancer formation/growth
- Larger effects on retinal
- Reduces ROS in CNS
- Cardiovascular protection
- Enhances metabolism (for the better?)
- LCM?

Promising Future for PEDF?

- “Hence, there is a strong impetus to develop new PEDF-based agents for ocular disease, to replace or supplement VEGF inhibitors, especially because PEDF also possesses neuroprotective properties and the ability to sustain the neuronal [22,103,134] and RPE SC niches. To date, ocular disease appears to be the most promising clinical application of PEDF.” — Crawford SE, et al. (2013)

- Although PEDF exhibits effective therapeutic potential, its application is limited by its short half-life, unstable pharmacology, and administration pathway. — Bai YJ, et al. (2012)

Topical Anti-VEGF Therapy

- Avastin (Bevacizumab) is eyedrop form!
- Has been shown to penetrate through corneal tissues into anterior chamber
- Avastin drops used QID Q7D x 2 weeks caused 80% regression in 3 of 8 patients in one study
- Decreases risk of VR, traumatic cataract, BD, endothelialitis, etc.
- Still in its infancy....

- Also, for central neuroaxonalization too!
- Acute/chronic forms
- Anterior segment cancers

Phenylephrine & Risk of Increased Blood Pressure

Is the fear justified???

- Developed in 1933 from EPI
- Potent vasoconstrictor, alpha-1 agonist
  - No late pupillary reactivity
  - Dilation of pupil without cycloplegia
  - Negligible effect on IOP
- Maximum duration of action - 4-7 hrs
- Peripheral vasoconstriction can lead to rapidly elevated BP in some patients
- Systolic and diastolic is affected
**Can PHE cause increased BP? How likely is this to happen if it does?**

- First episodes of elevated BP from topical PHE were in 1956
  - Some authors say: PHE has no effect on BP
  - Some authors say: Mixed PHE-induced HTN responses
  - Others say: definite increases in BP with topical PHE

- Mass confusion across the board...

**Worst Cases…**

- Cotton pledget 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

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**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; 20-60 minutes duration
- HTN effects coincide with peak tissue and plasma levels
- 2.5% PHE = 10% PHE with dilution
- Orthostatic hypotension pts at higher risk
- Observation hypotonicity?

- End-Organ Damage:
  - SAH
  - Aneurysm rupture
  - *Papilledema
  - Pulmonary edema
  - MI
  - CVA

**10% PHE Total Risk of Adverse Events**

<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>1864</td>
<td>7.56% (n=141/1864)</td>
<td>14.70% (n=274/1864)</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>

**2.5% PHE Total Risk of Adverse Events**

<table>
<thead>
<tr>
<th></th>
<th>Total (n)</th>
<th>2.5% PHE Severe</th>
<th>2.5% PHE Increased BP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults</td>
<td>2210</td>
<td>0.18% (n=4/2210)</td>
<td>0.70% (n=15/2155)</td>
</tr>
<tr>
<td>Pediatrics</td>
<td>363</td>
<td>0.28% (n=1/363)</td>
<td>4.98% (n=12/241)</td>
</tr>
</tbody>
</table>

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**Risk of causing increased blood pressure in adult patients**

<table>
<thead>
<tr>
<th>10% PHE</th>
<th>Total (n)</th>
<th>Risk of causing increased blood pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 gtt OU</td>
<td>460</td>
<td>2.17% (n=10/460)</td>
</tr>
<tr>
<td>2 gtt OU</td>
<td>181</td>
<td>11.05% (n=20/181)</td>
</tr>
<tr>
<td>3+ gtt OU</td>
<td>761</td>
<td>26.81% (n=204/761)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2.5% PHE</th>
<th>Total (n)</th>
<th>Risk of causing increased blood pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 gtt OU</td>
<td>767</td>
<td>0.65% (n=5/767)</td>
</tr>
<tr>
<td>2 gtt OU</td>
<td>414</td>
<td>1.93% (n=8/414)</td>
</tr>
</tbody>
</table>

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**10% PHE Risk of causing increased blood pressure in pediatric patients**

<table>
<thead>
<tr>
<th>10% PHE</th>
<th>Total (n)</th>
<th>Risk of causing increased blood pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 gtt OU</td>
<td>4</td>
<td>100% (n=4/4)</td>
</tr>
<tr>
<td>2 gtt OU</td>
<td>20</td>
<td>100% (n=20/20)</td>
</tr>
<tr>
<td>3+ gtt OU</td>
<td>20</td>
<td>65% (n=13/20)</td>
</tr>
</tbody>
</table>

**2.5% PHE Risk of causing increased blood pressure in pediatric patients**

<table>
<thead>
<tr>
<th>2.5% PHE</th>
<th>Total (n)</th>
<th>Risk of causing increased blood pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 gtt OU</td>
<td>31</td>
<td>0% (n=0/31)</td>
</tr>
<tr>
<td>2 gtt OU</td>
<td>0</td>
<td>Unable to quantify with available studies</td>
</tr>
<tr>
<td>3+ gtt OU</td>
<td>211</td>
<td>1.11% (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 synchiae 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 peds

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

So..... is the fear justified???

Ethambutol Ocular Toxicity Risk Calculations

- Antimicrobial medication: predominantly bacteriostatic
- Treatment: minimum of 6 months in most cases
- Drug most often implicated in optic neuropathy
  - D-Isomer = therapeutic form
  - L-Isomer = toxic form

- Loading dose initially 25 mg/kg/day x 2 mo
- Maintenance dose = 15-20 mg/kg/day
- Ideal dose = 15 mg/kg/day
- >25 mg/kg/day = high doses
- No safe dose of EMB has been reported!
- Toxicity comes from less (L) form, therapeutic effect from dextro (D) form isomer

Retrobulbar Optic Neuritis

- EMB causing demyelinating effect
- EMB Toxicity
  - Central
    - Acuity, color, sensitivity, reading difficulty, option vision defects, VF defects within central 10°
  - Monocular
  - Paresthesia
  - Peripheral
    - VF defects outside central 10°

EMB Toxicity

- VA = normal to NLP
- Onset = 2-12 months, average 6-7 months
  - After 3 months has been reported
- Visual Recovery: 40-50% after 2-6 months of discontinuation
  - Unpredictable thereafter
- Age >40 YO = lower rate of recovery
- Daily dose x1.4 duration of treatment
- Temporal optic nerve atrophy
  - Highest metabolic demand here (papillo-macular bundle)
  - Return line = mitochondrial dysfunction. 2 EMB toxicity
Example #1

- A 150 lbs male who is taking 1000 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 based on this dose?

\[
\frac{150 \text{ lbs}}{2.2 \text{ lbs}} = 68.18 \text{ kg of body weight}
\]

\[
1000 \text{ mg} \times \frac{1}{68.18 \text{ kg}} = 15 \text{ mg/kg/day}
\]

- \(1.31\% \) risk

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### 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>Risk Range</th>
<th>Mean Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>15 mg/kg/d</td>
<td>0.62-2%</td>
<td>1.31%</td>
</tr>
<tr>
<td>17.85 mg/kg/d</td>
<td>1.5%</td>
<td>1.5%</td>
</tr>
<tr>
<td>20 mg/kg/d</td>
<td>3.6-3%</td>
<td>4.65%</td>
</tr>
<tr>
<td>25 mg/kg/d</td>
<td>2.2-9.4%</td>
<td>5.8%</td>
</tr>
<tr>
<td>60 mg/kg/d</td>
<td>15-18.6%</td>
<td>16.8%</td>
</tr>
<tr>
<td>100 mg/kg/d</td>
<td>15-33.3%</td>
<td>24.15%</td>
</tr>
</tbody>
</table>

The Calculation

\[
\frac{\text{Body Weight (lbs)}}{2.2 \text{ lbs}} = \frac{\text{weight in kilograms}}{\text{Total daily dose (mg)} \times \frac{1}{\text{body weight (kg)}} = \text{dose of mg/kg/day}}
\]
Example #2:

A 100 lbs female who is taking 1600 mg Ethambutol daily for her *Mycobacterium tuberculosis* 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 \( \div 2.2 \text{ kg} \) = 45.45 kg
- 1600 mg \( \times \frac{1}{45.45 \text{ kg}} \) = 35 mg/kg/day
- \(-16.8\%\) risk

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.

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<th>17.85 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>3.6-3.9%</td>
<td>2.2-9.4%</td>
<td>15-18.6%</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>4.6%</td>
<td>5.8%</td>
<td>16.8%</td>
<td>24.1%</td>
<td>45%</td>
</tr>
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</table>

Rho-Kinase Inhibitors

- Aka “ROCK-inhibitors”
- Lower IOP ~25% ; 3-6 mmHg in most studies
- One drug QD-BID depending on the drug
- Biggest SE = hyperemia/redness from vasodilation effect; up to 65% cases
- 4 main effects:
  - significant IOP-lowering effects
  - improvement in ocular blood flow
  - inhibition of postoperative scarring
  - promotion of retinal ganglion cell survival and axon regeneration.

Molecular MOA...

- Pathology = Upregulation of RhoK
  - ROCK is a ROCK-kinase that phosphorylates of myosin light chains leading to increased contractility of those fibers in TM → increased cell-to-cell adhesion in TM
  - Reduced Aq outflow
  - Rho/kinase A is most prevalent elevated Rho/GTPase in glaucomatous eyes
- Drug properties:
  - ROCK Inhibitors → Increased Aq outflow

ROCK Inhibitors’ MOA
Rho-Kinase Inhibitors MOA

- Site of action = TM → increase spaces between TM cells
- Specifically, in the juxtacanalicular portion of TM

Bottom Line: ROCK inhibitors make TM more porous!

Pipeline Drugs: Rho-Kinase Inhibitors

- **Rhopressa**
  - Combination drug: ROCK inhibitor + NET inhibitor
  - NET = norepinephrine transmitter
  - Increases TM outflow, decreases aqueous production, decreases EVP

- **Roclatan**
  - Rhopressa + Latanoprost
  - OD dosing
  - Lowers IOP by ~34%

Neuroprotection???

- Increased blood flow (inhibition of Ca channels) → vascular relaxation
- Increased survival by 1/3 in one study of crush optic nerves in mice
- TBD...

Questions???

- Thank you!
- chorgman@sco.edu

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SOUTHERN COLLEGE OF OPTOMETRY

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