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

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SOUTHERN COLLEGE OF OPTOMETRY

Disclosures:

I have no disclosures to report.

Ground Rules…

- References/sources available upon request
- I'm not perfect…
- Please email me with questions:
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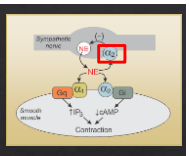
Alphagan (Brimonidine) & Pupillary Miosis???

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**

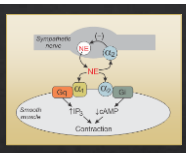
McDonald et al, J Cataract Surg 2001, 27:560-564

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?



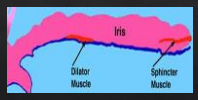
In the sympathetic system:
- Norepinephrine released adrenergic nerve terminals

- Stimulating alpha-1 receptors ->
  - Mydriasis
  - By contraction 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 ?

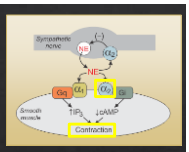
- **Brimonidine**
  - **has no effect the cholinergic driven sphincter muscle in photopic conditions (PNS)**
  - **There is a less obvious size difference with and without brimonidine**



- **Therefore, photopic pupil size is relatively normal**

Alphagan (Brimonidine) & Redness Reliever

Brimonidine tartrate 0.025%



- Diluted brimonidine solution → vasoconstriction
  - Post-synaptic junction
- Just completed Phase 3 trials (Bausch & Lomb)
- 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
- 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

Topical Timolol & Superior Oblique Myokymia

Dx = Superior Oblique Myokymia

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

- Defn: monocular quivering/firing of superior oblique
- Sx: spontaneous monocular diplopia, quivering/jumping of vision, monocular oscillopsia, key is *monocular* nature
- Sn: low amplitude, high frequency intorsion 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

SOM Tx Options

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

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: hypothesized that enough drug was absorbed ***systemically*** through conjunctival blood vessels to elicit its effect (systemic theory)

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 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"

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** →

Borgman CJ. Topical timolol in the treatment of monocular oscillopsia secondary to superior oblique myokymia: a review. J Optom. 2014;7:68-74.

2. **Eyelid Myokymia** →

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

Mineralcorticoid Receptor Antagonists & CSR

Central Serous Chorioretinopathy

- Circumscribed serous RD; usually macular region
  - Pathophysiology = unknown
- M>F (72-88% of time); 30-50 YO age range normally
- Bilateral in 40%
- Most acute episodes resolve in 2-3 months on own
- Recurrences common (up to 50%) → chronic CSCR in 5-10% of cases
  - Chronic CSR = >3-4 mo duration in most studies
- Historically, corticosteroids can aggravate CSCR; unknown MOA
- Exogenous/endogenous cortisol, Cushing's syndrome, psychological stress, Type A, pregnancy = risk factors
  - Males, HTN, collagen vascular diseases, H.Pylori infection
- PDT, anti-VEGF, CAI's , beta-blockers have been tried with varied success

OCT Evidence of MOA?

- New evidence: diffuse choroidal thickening in CSCR eyes (and contralateral eyes)
  - Choroidal vascular hyperpermeability!
  - How does hyperpermeability occur?
    - Unknown still

Corticosteroids

- Produced by adrenal cortex
1. Mineralcorticoid = aldosterone
   - Bind to both mineralcorticoid (MR) and glucocorticoid receptors (GR)!
2. Glucocorticoid = cortisol
   - Bind to both mineralcorticoid and glucocorticoid receptors too!

- Cross binding to each receptor! Equal affinity for both!
- MOA: Excess cortisol spills over to activate MR receptors as well
- Choroid has both MR and GR
- Glucocorticoids & Mineralcorticoids both induce choroidal enlargement/thickening and cause vessel dilation and leakage which can overcome RPE's defenses → neurosensory detachment

Eplerenone (Inspra)

- FDA-approved in 2002 for HTN; 2003 for CHF
- **Oral mineralcorticoid/aldosterone receptor antagonist**
  - Competitive antagonist with high selectivity of MR; potassium sparing diuretic
- Reverses "endothelial vasodilatory potassium channel (KCa2.3)" activation in choroid
  - Stops/reverses choroidal thickening/leakage; down regulates KCa2.3
  - KCa2.3 only is expressed in choroid, not retina!
  - This is why MCR antagonists do not induce retinal 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**
- Follow up 1 month, then 3 months; repeat OCT

Mineralcorticoid 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 mineralcorticoids and glucocorticoids

Eplerenone vs. Spironolactone

- Both are mineralcorticoid receptor blockers!
- Both are postassium-sparing diuretics!
  - Risk of hyperkalemia
- Eplenerone has 10-20x lower affinity for MR than spironolactone
- However, eplerenone has a much higher specificity for MR without antiandrogen SE's
- Eplenerone is best choice with the least probably SE's at this time between the two.

How effective is Eplerenone on CSCR?

- Reduced SRF within 1 month = 25-71%
- Reduced SRF within in 3 months = 93%
- Complete resolution within 3 months= 64-67%
- *"It's relatively limited adverse effect profile and high selectivity and specificity (to the mineralcorticoid/glucocorticoid receptors) make eplenerone an ideal treatment modality for CSCR."*
  - Salz DA, et al. 2015 Ophth Surg Lasers Imag Ret.

Bottom Line..

- **Consider Eplerenone in CSCR lasting >3-4 months**
- 25mg daily x 1 week then 50 mg PO daily for up to 3 months
  - Tx lasted until resolution of fluid or 3 months of treatment
- Monitor serum potassium levels; co-manage with PCP
  - Measure serum potassium levels monthly
  - Discontinue med if:
    - Kalemia increase of >5 mmol/L
    - Creatinine clearance rate decrease of <60 mL/minute
- Likely best avoided in patients with renal problems
- Monitor q4-6 weeks while on medication with OCT's

New Direction…

What is cheapest way to maximum meds for glaucoma?

- 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 with the least amount of drops???

- 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% → $34.06
- Pred Acetate 1% → $29.63
- Dexamethasone 0.1% → $23.00
- Tobramycin → $4.00
- Polymyxin/TMP → $4.00

} TOTAL: **$27.00/month**

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

- Pred-G (brand) → $126.51
- Tobramycin/Dexamethasone → $55.54
- Tobramycin/Loteprednol (Zylet) → $210.28
- Neomycin/Polymyxin/Dexamethasone → $4.00

TOTAL: **$4.00/month**

$4 List of Generics Available

Antihistamine	NSAID's	ABx	Antiviral	Steroids
Loratadine	Naproxen	Cephalexin	Acyclovir	Prednisone
	Indomethacin	Amoxicillin		Dexamethasone
	Ibuprofen	Ciprofloxacin		
	Meloxicam	SMZ/TMP		

Topical ABx	Glaucoma	Steroids	Combos
Gentamicin	Timolol	Triamcinolone	Maxitrol
Tobramycin	Levobunolol		
Polymyxin/TMP			

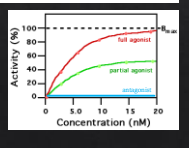
Additional Resource for Cheap Meds:
Borgman CJ. Many common conditions respond to inexpensive treatment options. *Primary Care Optometry News*. January 2015.

Abilify & Blurry Vision?

Aripiprazole (Abilify)

- Atypical antipsychotic medication
- Dopamine receptors (D2 & D3) → partial agonist
- Serotonin receptors (1A) → partial agonist
- Serotonin receptor (2A) → antagonist

- Schizophrenia
- Schizoaffective 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 spasm
  - ciliary body effusion,
  - ciliary spasm
  - increase in thickness of the lens and peripheral uveal effusion (3,5).
  - Ciliary body rotation and edema resulting in forward movement of iris lens diaphragm → acute myopia

Borgman's Theoretical MOA???

Relative Abundance of 5HT Receptor Subtype mRNA Signals

	$5HT_{2A}$	$5HT_{2B}$	$5HT_{2C}$	$5HT_3$	$5HT_4$	$5HT_5$	$5HT_6$	$5HT_7$
Iris	+++	+++	--	+	+	++	+	++
Ciliary body	+++	+++	++	++	++	++	--	+++
h-TM cells	+++	+++	+	--	--	+	--	+

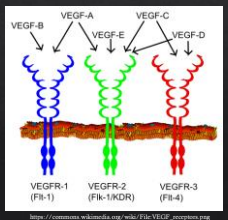
- Studies show:
  - Increased levels of serotonin → increased sympathetic innervation → mydriasis!
  - SSRI's and/or MAOI's

- Abilify (aripiprazole) is a serotonin receptor blocker (5-HT2A receptor)
- Decreased levels of serotonin → decreased sympathetic innervation → miosis & accomm
- **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



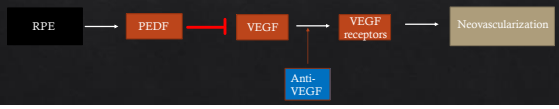
https://commons.wikimedia.org/wiki/File:VEGF_receptors.png

Intravitreal anti-VEGF Injections…

- Avastin, Lucentis, Eyelea
- Used as monotherapy and/or in combination therapy
- MOA: Bind to free-floating VEGF molecule to prevent attachment to endothelial surface receptors
  - By definition, do nothing for underlying disorder…
- Have been shown to stimulate regression of neo within 1-2 days!
- Short-half lives (~20 days); wear off over time

New: Pigment epithelium-derived factor (PEDF)

- Potent endogenous, broad-acting angiogenesis inhibitor
  - MOA: Inhibits formation of VEGF
- Targets new blood vessels with no measureable effect on mature blood vessels!
- Homeostatic balance between VEGF and PEDF
  - Increased VEGF = Decreased PEDF



Other effects of PEDF…

- Neuroprotection in CNS
  - Eyes included! Glaucoma?
  - Protection from NMDA, glutamate
- Reduces ischemia in retinal tissues
- Inhibits cancer formation/growth
  - Largest effect on metastasis!
- Reduces ROS in CNS
- Cardiovascular protection
- Enhances metabolism (for the better!)
  - DM??

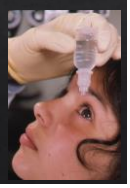
Promising Future for PEDF?

- "Hence, there is a strong impetus to develop new PEDF-based agents for ocular disease, to replace or supplement VEGF inhibitors, especially because of 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." --- Craword 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

Topical anti-VEGF therapy???

- Avastin (bevacizumab) in eyedrop form!
- Has been shown to penetrate through cornea tissues into anterior chamber
- Avastin drops used QID OU x 2 weeks caused iris neo regression in 3 of 8 patients in one study
- Decreases risks of VH, traumatic cataract, RD, endophthalmitis, etc.
- Still in its infancy…..
- Also, for corneal neovascularization too!
  - Acid/alkaline burns
  - Anterior segment cancers



Phenylephrine & Risk of Increased Blood Pressure

Is the fear justified???

Phenylephrine Review…

- Developed in 1933 from EPI
- **Potent vasoconstrictor; alpha-1 agonist**
  - No beta receptor activity at all
  - Dilation of pupil without cycloplegia
  - Neglible effect on IOP
- Maximum dilation = 15-90 minutes
- Maximum duration of action = 6-7 hrs
- Peripheral vasoconstriction can lead to rapidly elevated BP in some patients
  - Systolic and diastolic are 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 yet say: definite increases in BP with topical PHE
  - Mass confusion across the board…

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 dilation
- Orthostatic hypotension pts at highest risk?
  - Denervation hypersensitivity?

- Sn/Sx:
  - HA
  - Tachycardia
  - Chest pain
  - Palpitations
  - Perspiration
  - Nausea/vomiting
  - SOB
  - Reflex bradycardia/hypotension
- End-Organ Damage:
  - SAH
  - Aneurysm rupture
  - *Papilledema
  - Pulmonary edema
  - MI
  - CVA

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

10% PHE Total Risk of Adverse Events

	Total (n)	10% PHE Severe		10% PHE Increased BP	
Adults	1864	7.56%	(n=141/1864)	14.70%	(n=274/1864)
Pediatrics	44	11.36%	(n=5/44)	84.09%	(n=37/44)

2.5% PHE Total Risk of Adverse Events

	Total (n)	2.5% PHE Severe		2.5% PHE Increased BP	
Adults	2210	0.18%	(n=4/2210)	0.70%	(n=15/2155)
Pediatrics	363	0.28%	(n=1/363)	4.98%	(n=12/241)

Note: numbers based on 80+ articles on HTN & PHE risk

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

	Total (n)	Risk of causing increased blood pressure in adult patients	
10% PHE---1 gtt OU	460	2.17%	(n=10/460)
10% PHE---2 gtts OU	181	11.05%	(n=20/181)
10% PHE---3+ gtts OU	761	26.81%	(n=204/761)

	Total (n)	Risk of causing increased blood pressure in adult patients	
2.5% PHE---1 gtt OU	767	0.65%	(n=5/767)
2.5% PHE---2+ gtts OU	414	1.93%	(n=8/414)

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

	Total (n)	Risk of causing increased blood pressure in pediatric patients	
10% PHE---1 gtt OU	4	100%	(n=4/4)
10% PHE---2 gtts OU	20	100%	(n=20/20)
10% PHE---3+ gtts OU	20	65%	(n=13/20)

	Total (n)	Risk of causing increased blood pressure in pediatric patients	
2.5% PHE---1 gtt OU	31	0%	(n=0/31)
2.5% PHE---2 gtts OU	0	Unable to quantify with available studies	
2.5% PHE---3+gtts OU	211	7.11%	(n=15/211)

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 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???

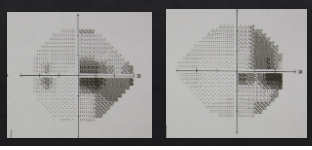
Ethambutol Ocular Toxicity Risk Calculations

Ethambutol

- Antituberculosis medication; predominantly bacteriostatic
- Treatment: minimum of 6 months in most cases
- Drug most often implicated in toxic 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 levo (L)-form; therapeutic effect from dextro (D)-form isomer

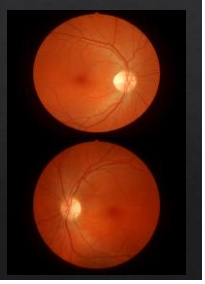
Retrobulbar Optic Neuritis

- EMB causing demyelinating effect
- EMB Toxicity
  - Central
    - Acuity, contrast sensitivity, reading difficulty, color vision defects, VF defects within central 10°
    - Most devastating
  - Peripheral
    - VF defects outside central 10°



EMB Toxicity

- VA = normal to NLP
- Onset = 2-12 months, average 6-7 months
  - after 36 months has been reported
- Visual Recovery: 40-50% after 2-8 months of discontinuation
  - Unpredictable though…
- Age: >60 YO = lower rate of recovery
- Daily dose >> duration of treatment
- Temporal optic nerve atrophy!
  - Highest metabolic demand here (papillo-macular bundle)
  - Bottom line → mitochondrial dysfunction 2° EMB toxicity



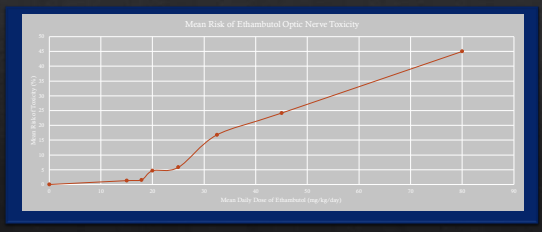
$$\frac{Body\ Weight(lbs)}{2.2\ lbs} = weight\ in\ kilograms$$

$$Total\ daily\ dose\ (mg)\ x \frac{1}{body\ weight\ (kg)} = dose\ of\ mg/kg/day$$

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]

Daily Dose	15 mg/kg/day	17.85 mg/kg/day	20 mg/kg/day	25 mg/kg/day	30-35 mg/kg/day	40-50 mg/kg/day	60-100 mg/kg/day
Risk Range	0.62-2%	1.5%	3-6.3%	2.2-9.4%	15-18.6%	15-33.3%	40-50%
Mean Risk	1.31%	1.5%	4.65%	5.8%	16.8%	24.15%	45%

Mean Risk of Ethambutol Optic Nerve Toxicity



The Calculation

$$\frac{Body\ Weight(lbs)}{2.2\ lbs} = weight\ in\ kilograms$$

$$Total\ daily\ dose\ (mg)\ x \frac{1}{body\ weight\ (kg)} = dose\ of\ mg/kg/day$$

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 his risk of developing ocular toxicity based on this dose?
- $\frac{150\ lbs}{2.2\ kg} = 68.18\ kg\ of\ body\ weight$
- $1000\ mg\ x \frac{1}{68.18\ kg} = 15\ mg/kg/day$
- ~1.31% 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[1,2,4,6-8,12-14,22,24-26,28-30,38-46]

Daily Dose	15 mg/kg/day	17.85 mg/kg/day	20 mg/kg/day	25 mg/kg/day	30-35 mg/kg/day	40-50 mg/kg/day	60-100 mg/kg/day
Risk Range	0.62-2%	1.5%	3-6.3%	2.2-9.4%	15-18.6%	15-33.3%	40-50%
Mean Risk	1.31%	1.5%	4.65%	5.8%	16.8%	24.15%	45%

Example #2:

- 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?
- $\frac{100\ lbs}{2.2\ kg} = 45.45\ kg$
- $1600\ mg\ x \frac{1}{45.45\ kg} = 35\ mg/kg/day$
- ~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[1,2,4,6-8,12-14,22,24-26,28-30,38-46]

Daily Dose	15 mg/kg/day	17.85 mg/kg/day	20 mg/kg/day	25 mg/kg/day	30-35 mg/kg/day	40-50 mg/kg/day	60-100 mg/kg/day
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Recommendations…

1. Prior to starting EMB → Baseline exam
2. 1 month later
3. q3-6 months while on EMB
4. D/c with any signs of toxicity

- Acuity, Pupils, DFE, HVF, Fundus photos, OCT, color vision at every visit
  - Consider both 10-2 & 24/30-2 protocols
- Communicate findings (and risk) to prescribing PCP!


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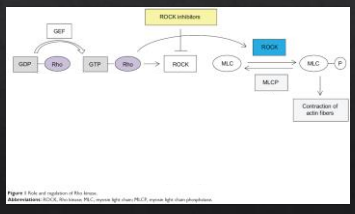
Rho-Kinase Inhibitors

- **Aka "ROCK-inhibitors"**
- **Lower IOP ~25% ; 3-6 mmHg in most studies**
- **One drop 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-1 and ROCK-2 agonism leads to phosphorylation of myosin light chains leading to increased contractility of those fibers in TM → increased cell-to-cell adhesion in TM
  - **Reduced AH outflow**
  - Rho-Kinase A is most prevalent/elevated RhoGTPase in glaucomatous eyes
- **Down-regulation:**
- ROCK Inhibition → **Increased AH 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

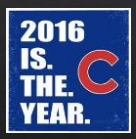
- **Rhopressa**
  - Combination drug: ROCK inhibitor + NET inhibitor
    - NET = norephinephrine transmitter
    - Increases TM outflow, decreases aqueous production; decreases EVP
- **Roclatan**
  - Rhopressa + Latanoprost
  - QD dosing
  - Lowers IOP by ~34%

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!
- cborgman@sco.edu



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