GLAUCOMA PHARMACOLOGY A-Z

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Disclosures

Eric E. Schmidt, O.D.

Aerie – Advisory Board
Allergan – Consultant, Advisory Board
AMO – Consultant, Advisory Board
B & L – Advisory Board/Speaker bureau
Glaukos – Consultant
Sensimed – Advisory Board
Zeiss – Speaker Bureau
SELECTING THERAPY

- Goals of primary therapy
  - Achieve lowest IOP on monotherapy
  - High response rate—few to no nonresponders
  - Maintain consistent IOP lowering
  - Obtain patient compliance and adherence by meeting their goals and expectations

- Building-block approach to medical therapy
  - Establish the strongest foundation prior to resorting to adjunctive therapy
PROSTAGLANDIN ANALOGS

- Lower IOP by enhancing uveoscleral outflow
- They also reduce episcleral venous pressure
- PGAs work by causing up to a 26% reduction in resistance to outflow
- Breaks down collagen in the uveoscleral meshwork
- Create new channels for outflow
PGA

- QHS dosing
- Long duration of action
- Flatten diurnal curve
- Effective on trough and peak IOP
- No systemic side effects
- Little tachyphylaxis

PROSTAGLANDINS 2017

- Bimatoprost (Lumigan) 0.01%
- Latanoprost (Xalatan)
- Travaprost, Travaprost Z (Travatan, Travatan Z)
- Zioptan(tafluprost)

- Vyzulta??
- Xelpros??
9 PROSTAGLANDIN SIDE EFFECTS

- Conjunctival hyperemia: Severe hyperemia
  - Lumigan 3.5%
  - Travatan 1.5%
  - Xalatan <1%
  - Vyzulta?!

- Is this a transient phenomenon?
- Is it an allergic conjunctivitis?
- Is it worth stopping the drop?

10 CONJUNCTIVAL HYPEREMIA

- PGAs have an effect on EP receptors which are vasodilators

- The stronger the drug binds to that receptor the more pronounced the vasodilation effect will be –
  Oh Really!!

- Will switching from 1 PGA to another decrease the hyperemia effect?
PROSTAGLANDIN SIDE EFFECTS

- Iris pigmentation
  - Is it reversible?
  - Is it pre-cancerous?
- Xalatan – 6.7% @ 6mths
  16% @ 12mths
- Travatan – 3% @ 12 mths
- Lumigan – 1.9% @ 12mths

- SO?

OTHER PROSTAGLANDIN SIDE EFFECTS

- CME
- Uveitis
- Reactivation of HSK
- Hypertrichosis
- Periorbital skin darkening
- Periorbital fat atrophy

- One must take into consideration the benefits of low IOP with the risks of the side effects
PROSTAGLANDINS

- Oh sure, we know they are good, but just how good are they?
  - Average IOP drop of 34%
  - Improved compliance
  - Excellent safety profiles

- In general, PGAs are the initial therapy of choice.
BIMATOPROST AND TIMOLOL
12-MONTH STUDY

Mean IOP at Month 12

Timolol BID (n = 241)
Bimatoprost QD (n = 474)

*P < .001 vs timolol

Baseline mean IOP comparable between groups
Timolol: 25.8, 24.1, 23.2, 22.4 (8 AM, 12 PM, 4 PM, 8 PM; mm Hg)
Bimatoprost: 26.0, 24.7, 23.8, 22.1 (8 AM, 12 PM, 4 PM, 8 PM; mm Hg)

Target Pressures at Month 12

*P < .010 vs timolol

Percentage of Patients Reaching Target IOP at 10 AM, Month 12

BIMATOPROST AND TIMOLOL EFFICACY OVER 4 YEARS

Mean IOP Across 48 Months

- Timolol BID (n = 35)
- Bimatoprost QD (n = 78)

*P ≤ .043

CLINICAL COMPARISON TRIALS OF THE ONCE-DAILY PGA

- Evaluation of intra-class differences in efficacy and safety
- Seven published, prospective, randomized, investigator-masked, parallel-group studies
- Trials varied in duration, patient selection and characteristics, and methods of data analysis
BIMATOPROST AND TRAVOPROST

<table>
<thead>
<tr>
<th>Sponsor</th>
<th>Pfizer</th>
<th>Allergan</th>
<th>Allergan</th>
</tr>
</thead>
<tbody>
<tr>
<td>Length</td>
<td>12 weeks</td>
<td>3 months</td>
<td>6 months</td>
</tr>
<tr>
<td>Bimatoprost</td>
<td>n = 136</td>
<td>n = 16</td>
<td>n = 76</td>
</tr>
<tr>
<td>Travoprost</td>
<td>n = 138</td>
<td>n = 15</td>
<td>n = 81</td>
</tr>
<tr>
<td>Latanoprost</td>
<td>n = 136</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Barrish et al also included study arm with bimatoprost (n = 136).†Study population comprised of African-American patients.*


BIMATOPROST AND TRAVOPROST: 12-WEEK STUDY

Mean IOP at Week 12

Baseline mean IOP comparable between groups

Travoprost: 25.5, 23.8, 22.8, 22.0 (8 AM, 12 PM, 4 PM, 8 PM; mm Hg)
Bimatoprost: 25.7, 23.8, 22.8, 22.3 (8 AM, 12 PM, 4 PM, 8 PM; mm Hg)

BIMATOPROST AND TRAVOPROST: 6-MONTH STUDY

Mean IOP at Month 6

Baseline mean IOP comparable between groups
Travoprost: 24.4, 22.6, 22.0 (9 AM, 1 PM, 4 PM; mm Hg)
Bimatoprost: 24.6, 22.6, 22.2 (9 AM, 1 PM, 4 PM; mm Hg)

P = .038
P = .095
P = .099

% of Patients Achieving ≥ 20% IOP Reduction at 9 AM

Bimatoprost (n = 71)
Travoprost (n = 70)

P = .058
BIMATOPROST AND TRAVOPROST:
6-MONTH SAFETY RESULTS

- Both medications were well tolerated
- Most common adverse event: ocular redness
  - 16 patients (20.8%) in the bimatoprost group and 12 patients (14.8%) in the travoprost group ($P = .326$)
- Ocular itching reported for 7.4% of travoprost patients and 2.3% of bimatoprost patients ($P = .278$)
- Treatment-related adverse events leading to patient discontinuations
  - 8 patients in the travoprost group exited early: 4 for lack of efficacy, 2 for ocular redness and lid erythema, 1 for ocular dryness and itching, and 1 for allergic symptoms
  - 2 patients in the bimatoprost group exited early: 1 for blurry vision and 1 for ocular redness and lid erythema

BIMATOPROST AND LATANOPROST:
3 MONTH STUDY

Baseline mean IOP comparable between groups
Latanoprost: 25.7, 23.7, 23.0, 22.3 (8 AM, 12 PM, 4 PM, 8 PM; mm Hg)
Bimatoprost: 25.7, 23.8, 22.8, 22.3 (8 AM, 12 PM, 4 PM, 8 PM; mm Hg)

Study population: previously treated patients (approximately 50% on latanoprost at screening)
Among-group differences not statistically significant; consistently lower mean IOP at 8 AM

Mean IOP at Week 12

Baseline mean IOP comparable between groups
Latanoprost: 25.7, 23.7, 23.0, 22.3 (8 AM, 12 PM, 4 PM, 8 PM; mm Hg)
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Mean IOP at Week 12
**BIMATOPROST AND LATANOPROST: 6-MONTH STUDY**

### Mean IOP at Month 6

<table>
<thead>
<tr>
<th>Time of Day</th>
<th>Baseline mean IOP (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>8 AM</td>
<td>Latanoprost: 24.9, 23.3, 22.5</td>
</tr>
<tr>
<td>12 PM</td>
<td>Bimatoprost: 25.0, 24.0, 22.6</td>
</tr>
<tr>
<td>4 PM</td>
<td></td>
</tr>
</tbody>
</table>

- Mean IOP consistently lower throughout the day with bimatoprost.


### Percentage of Patients Achieving ≥20% IOP Reduction

<table>
<thead>
<tr>
<th>Time of Day</th>
<th>Bimatoprost (n = 133)</th>
<th>Latanoprost (n = 136)</th>
</tr>
</thead>
<tbody>
<tr>
<td>8 AM</td>
<td>62%</td>
<td>61%</td>
</tr>
<tr>
<td>12 PM</td>
<td>62%</td>
<td>61%</td>
</tr>
<tr>
<td>4 PM</td>
<td>61%</td>
<td>50%</td>
</tr>
</tbody>
</table>

BIMATOPROST AND LATANOPROST: 6-MONTH SAFETY RESULTS

- Most common side effects:
  - Hyperemia (bimatoprost 44.4%; latanoprost 20.6%)
- Similar rates of discontinuation due to AEs
  - Bimatoprost: 4.5% overall; 2.3% for hyperemia
  - Latanoprost: 3.7% overall; 0.0% for hyperemia
- Uveitis: One patient in latanoprost group; no cystoid macular edema

BIMATOPROST AND LATANOPROST + TIMOPTIC-XE®: 6-MONTH STUDY

Mean Diurnal IOP Over 6 Months

Baseline mean diurnal IOP comparable between groups
Bimatoprost 23.5 mm Hg
Latanoprost / timolol gel 24.1 mm Hg

PROSTAGLANDINS

- All decrease IOP by increasing uveoscleral outflow
- All are effective at squashing the diurnal curve
- They have either no effect or a positive effect on retinal perfusion
- But does 1 work better than the others?

IOP REDUCING EFFECT

- According to package inserts:
  - Latanoprost – 6.7mm
  - Bimatoprost – 8.1mm
  - Travaprost – 7.1mm
XLT STUDY – PARRISH, PALMBERG, ET. AL.
(AJO, MAY 2003, VOL. 135, NO. 5)

• Multicenter study to compare IOP lowering efficacy of Bimatoprost vs Latanoprost vs Travaprost

• Also compared safety profiles of the 3 drugs

• Conclusions: All 3 drugs were comparable in their ability to lower IOP at all time periods.
  • Latanoprost exhibited greater ocular tolerability
ANOTHER WAY TO LOOK AT EFFICACY:

- % of IOP reduction –
  - Latanoprost – 27%
  - Unoprostone – 15%
  - Bimatoprost – 33%
  - Travaprost – 28%

- FYI: Timolol 24%
WHAT IS THEIR ABILITY TO LOWER IOP <17MM?

- Latanoprost – 49.5% of pxs
- Bimatoprost – 64%
- Travaprost – 56.3%

LOOK AT THEIR FAILURE RATE:

- Percent of pxs who didn’t reach their target IOP
  - Latanoprost – 14%
  - Bimatoprost- 6%
  - Travaprost – 8%

- SO?
WHAT IF:

• A patient failed on Xalatan?

• If switched to Lumigan, 57% achieved target IOP
• If switched to Travatan, 45.5% achieved target IOP

• SO?- Are all prostaglandins really created equal?


• Replaced Xalatan w/ Lumigan

• Results:
  • IOP <15mm dropped from 11% to 36%
  • IOP <18mm dropped from 33% to 66%
  • Mean IOP decrease of 3.4mm
ARE GENERICS REALLY AS GOOD AS BRANDED PRODUCTS?

WHAT ABOUT WHEN IT COMES TO PROSTAGLANDINS?

DROP STUDY – MEYER, 2014
WHAT ELSE IS NEW?

- Zioptan (Trafluprost) – Merck
  - Unit dose vial
  - QHS dosing
  - Unpreserved
  - Studies show 6-8 mm Hg drop in IOP from baseline of 24-26
  - Excellent safety profile
CLINICAL THOUGHTS ON ZIOPTAN

• Definite a kinder, gentler PGA

• Unit dose vials a perceived benefit

• Compliance enhanced?

• IOP decrease not as robust as other PGAs
FINAL PROSTAGLANDIN THOUGHTS

• They are additive to other G drugs but not with each other
• Travatan and Lumigan maintain target IOP 36hrs after instillation and significant IOP drop up to 84 hrs after instillation
• Does one really work better than the others on African-Americans?
• What about BID dosing?

A NEW PGA –AVAILABLE...NOW!!

• Latanoprostene bunod 0.024%
  • Nitric oxide donating prostaglandin
  • F2-alpha analog
• 1 drop QHS
• B & L
• Vyzulta – available 2018!!!
VYZULTA – LATANOPROST BUNOD 0.024%

- Nitric-oxide donating PGA
- B & L
- QD dosing
- Reduces IOP 7.5 – 9.1 mm- superior to timolol
- How does it compare to the other PGAs??
- How is it different??
- How is it better ??

VYZULTA

- Adding NO donor increases outflow through Schlemm’s Canal and t.m.
- Increases relaxation of these tissues
- Non-inferior to timolol (LUNAR Study)
- However…nearly twice as many eyes had IOP lowered >25% as compared to timolol
VYZULTA – MEDEIROS ET AL, AJO, 2016

- Additional 1.2mm lowering of nocturnal IOP
- Hyperemia rate-9%
- Eye irritation – 7.2%

LBN AND OPP

- LBN exhibited better ocular perfusion pressure than timolol, especially at night!!!
- Better IOP reduction at night as well

- Liu et al, AJO 2016
LATANOPROSTENE BUNOD (LBN)

- Phase 2 study
- Head to head study vs Xalatan
- 413 patients
- LBN consistently lowered IOP in a dose-dependent manner
- Significantly lower IOP than Xalatan at day 28 (also at day 7 and 14)
- .98mm Hg lower at all time points
- Slightly higher hyperemia rate

ONE MORE NEW PGA!!

- Xelpros (Sun Pharmaceuticals)
  - Latanoprost BAK-free drops
  - New delivery option
  - Multi dose bottle
  - Similar in efficacy to latanoprost
  - Has not been compared to Xalatan
  - What about side effect profile?
  - What about cost?
BETA-BLOCKERS

- 30 year history of successfully lowering IOP
- Reduces aqueous humor formation
- Adrenergic agonists
- Lowers IOP 22-28%
- Ocularly well tolerated
BETA-BLOCKERS

• Timolol maleate – Timoptic, Timoptic XE (1/2, 1/4 %)
• Carteolol – Ocupper 1% (Intrinsic sympathomimetic activity)
• Levobunolol – Betagan ½%
• Timolol hemihydrate – Betimol ¼, ½%
• Istalol ¼, 1/2% - QD dosing indication
• Betaxolol ¼% - cardioselective, safer?

BETA-BLOCKER SIDE EFFECTS

• Respiratory-
  • Fatigue, bronchospasm, SOB!
• Cardiac –
  • Lethargy, bradycardia, lower pulse rate
• CNS depression-
  • Impotence, confusion
• But how common are they?
LAMA STUDY (AJO 11/02)

- Conclusions:
  - ...identifies no scientific studies supporting the development of worsening claudication, depression, hypoglycemia, sexual dysfunction or impaired neuromuscular transmission
  - Recommends careful medical history and checking pulse rate and rhythm
- So?

BETA-BLOCKER SIDE EFFECTS

- Cardiac problems
  - Bradycardia
  - Hypotension
  - Exercise intolerance
  - Heart block

- Respiratory problems
  - Bronchospasm
  - Status asthmaticus
BETA-BLOCKER SIDE EFFECTS

• CNS
  • Often overlooked
  • ACID
    • Anxiety
    • Confusion
    • Impotence
    • Depression
  • General decreased affect

• Diabetic problems
  • Decreased sense of caloric need due to depressed adrenergic surge

• 22% of pts have contraindication to or significant side effect from beta-blocker
• Question, query and query some more!
• Be specific
• Remember the dose relationship so:
  • ¼% rather than ½%
  • QD rather than BID
• They are real (may be anecdotal)
THE BIGGEST PROBLEM WITH TOPICAL BETA-BLOCKERS?

• Decreased Perfusion To The Optic Nerve Head!!
• Especially At Night!!

BETA-BLOCKER DEBATE

• Are they still useful?
• As initial therapy?
• QD or BID?
• 0.25% or 0.5%?
• Gel or drop?
• Monocular therapy?
• How bad are the side effects really?
• Do systemic beta-blockers affect the efficacy of the drops?

• Tell me something good about beta-blockers!
ADRENERGIC AGONISTS

- Dual mechanism of action
  1. Reduce aqueous production
  2. Enhance outflow mechanisms
- 22-28% IOP reduction
- Short duration of action
- TID dosage
- Avoid in kids

BRIMONIDINE:
DUAL MECHANISM OF IOP LOWERING

- Enhances uveoscleral outflow
- Suppresses aqueous humor production (inflow)

MECHANISM OF ACTION OF BRIMONIDINE-PURITE®

- Complements PGAs because it decreases aqueous production
- Complements timolol because it increases uveoscleral outflow

BRIMONIDINE FORMULATION COMPARISON

<table>
<thead>
<tr>
<th></th>
<th>ALPHAGAN® P</th>
<th>ALPHAGAN®</th>
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<tbody>
<tr>
<td>Concentration of Brimonidine</td>
<td>0.1%</td>
<td>0.15%</td>
</tr>
<tr>
<td>pH</td>
<td>7.7</td>
<td>7.2</td>
</tr>
<tr>
<td>Preservative</td>
<td>PURITE®</td>
<td>BAK</td>
</tr>
<tr>
<td>Viscosity agent</td>
<td>Carboxymethylcellulose</td>
<td>Polyvinyl alcohol</td>
</tr>
<tr>
<td>Electrolytes</td>
<td>Potassium chloride, calcium chloride dihydrate, magnesium chloride hexahydrate</td>
<td></td>
</tr>
</tbody>
</table>
BENZALKONIUM CHLORIDE (BAK)

- Most commonly used preservative in glaucoma products
- BAK can accumulate and remain in ocular tissue
  - Has been shown to cause cytotoxic effects on the ocular surface in numerous studies
  (DeSaint, 2000; Gasset et al, 1974; Noecker, 2004)

PURITE® IS A GENTLE PRESERVATIVE

SEM of rabbit corneal epithelium (800X)

Untreated  PURITE® QID 7 days  BAK QID 7 days

The clinical significance of these data is unknown.

OCULAR BIOAVAILABILITY OF BRIMONIDINE IN DIFFERENT FORMULATIONS

Aqueous Humor Concentration in Rabbits

- Brimonidine-PURITE® 0.15% formulation shows bioavailability in the aqueous humor comparable to brimonidine 0.2% BAK

\[C_{\text{max}} (\mu g/mL)\]

\[*P = .04 \text{ vs brimonidine 0.15% BAK}\]

The clinical significance of these data is unknown.


MEAN IOP AT PEAK (10 AM)

- Brimonidine-PURITE® 0.15% (N = 372)
- Brimonidine 0.2%* (N = 376)

*Original ALPHAGAN®

**MEAN IOP AT TROUGH (8 AM)**

- Brimonidine-PURITE® 0.15% (N = 372)
- Brimonidine 0.2%* (N = 376)

**MEAN CHANGE FROM BASELINE AT MONTH 12**

ALPHAGAN® P 0.1% demonstrates IOP-lowering efficacy equivalent to ALPHAGAN® 0.2% over 12 months.
ADVERSE EVENTS TYPICALLY ASSOCIATED WITH BRIMONIDINE 0.2%* ARE LOWER WITH BRIMONIDINE-PURITE® 0.15%

BRIMONIDINE-PURITE® 0.15% HAS SIGNIFICANTLY LOWER INCIDENCE OF OCULAR ALLERGY

*Original ALPHAGAN®
EFFECT OF BRIMONIDINE-PURITE® 0.1% FORMULATION ON SAFETY

• Ocular surface exposed to 50% less drug with new formulation
  • Less allergy, redness, irritation
• Lower concentration also means fewer systemic effects as less drug enters nasolacrimal duct

BRIMONIDINE SIDE EFFECTS

• 10-20%
  • Hyperemia
  • Allergic conjunctivitis
  • Ocular pruritis
• 5-9%
  • burning sensation,
  • conjunctival folliculosis,
  • ocular allergic reaction,
  • oral dryness,
  • visual disturbance

• Do these worsen with time?
• How do you know if the drops are the culprit?
ALPHAGAN SYSTEMIC SIDE EFFECTS

• Dry mouth (~20%)
• Fatigue (1-2%)
• Drowsiness
• Decreased BP

• This drug can cross blood-brain barrier, esp in older and younger pxs

BRIMONIDINE QUESTIONS

• What is the correct dosage?
• Which of the 3 products should be prescribed?
• Can it be used as stand alone therapy?
• Effect on diurnal curve?

• What Happens If Hypersensitivity To 0.2% Brimonidine Occurs?
NEUROPROTECTION???

- Does it really exist?
- Does Alphagan promote neuroprotection?

FEKE ET AL, AJO 2014

- Effect of brimonidine on retinal vascular autoregulation and short-term visual function in NTG
FEKE STUDY

- Identified NTG pxs who had retinal blood flow changes upon postural change
- Those pxs were placed on Alphagan P 0.15% x 8 weeks then retested
- 14/17 demonstrated an improvement in postural induced retinal blood flow
- This did not show improvement in visual function

BRIMONIDINE MAY NOT WORK AT NIGHT

- Fan et al. J Glaucoma 2014; 23(5)
- Increased uveoscleral meshwork outflow during day with corresponding IOP reduction
- Drug has no effect on aqueous outflow, episcleral venous pessure or outflow facility
- There is a dramatic reduction in uveoscleral outflow at night
ALPHAGAN ALSO HAS A SHORT DURATION OF ACTION

- So what does this mean clinically??

CARBONIC ANHYDRASE INHIBITORS

- Lower IOP by reducing aqueous production
- Reduce IOP by 16-22%
- Sulfa drugs!!
- Dosage question – BID or TID?
- Are they useful as stand alone drugs?
CAI DIRECTORY

- Trusopt – Dorzolamide 2%
- Azopt - Brinzolamide 1%
- Oral CAI
  - Acetazolamide – Diamox 250, 500mg
  - Methazolamide – 25, 50mg

CAI SIDE EFFECTS

- ***Stinging***
- **Dryness**
- HA
- Bad taste
- Sulfa drug so:
  - Aplastic anemia?
  - Renal stones?
- What about Cosopt?
CAI MAKE WONDERFUL PARTNERS

- Feldman, et al 2006 –
- 1.5-1.8 mm lower IOP as compared to brimonidine 0.15% when added to travaprost
- This significance was present at all time points
- BID dosing

COMPANION STUDY #2

- When compared to brimonidine 2% adding them to Travaprost...
- IOP lowered by 13% w/ brimonidine
- IOP lowered by 23% w/ brinzolamide
COMPANION STUDY #3

- Stewart et al, 2006
- Compared to timolol 0.5% as additive to travaprost
- No difference at all between the 2 drugs
- CAI is effective at controlling night IOP spikes (TID?)

NEW GLAUCOMA DRUGS – TAPPING THAT PIPELINE!!!

- Nothing New For The Past 5 Years
- All Of A Sudden – BOOOM!

- Rhopressa
- Roclatan
- Vyzolta
- Trabodenoson
- Xelpros
- Bimatoprost SR
ROCK -INHIBITORS

- 2 drugs in the works – Aerie
- Rhopressa – Novel molecule
  - Works on different receptor sites so..
  - Effective IOP reduction with fewer side effects
  - No lash growth or skin darkening
  - Targets trabecular meshwork
- Roclatan – combo drug
  - Rhopressa and latanoprost
  - Availability 2017-2018

RHOPRESSA (NETARSUDIL) – AERIE PHARMACEUTICALS

- New class of drugs – Rho-kinase inhibitor
- MOA – “Triple Action”
  - relaxes trabecular meshwork similar to pilocarpine (enhances outflow)
  - lowers episcleral venous pressure
  - blocks fibrotic response at t.m.(increases perfusion)
- QD dosing
- Looks especially effective at IOP 25 mmHg or less
- 4th Quarter 2017??
WHAT'S TO LIKE ABOUT RHOPRESSA?

• New MOA so… it is absolutely different
• It should be additive
• Definitely works better at lower IOP

• What about side effects?
  • High rate of hyperemia ~50% (80% mild and transient)
  • Conj hemorrhages – 10%
  • Reduced level of BAK

ROCLATAN – AERIE

• Fixed Combination drug – Rhopressa + latanoprost
• QD dosing
• “Quadruple acting” MOA – (adds increased uveoscleral outflow)
• IOP lowering better than either of its components
• Potential to be very effective – lowered IOP an additional 2-3 mm
  compared to Rhopressa (and other PGAs)

• Currently in Phase 3
• Anticipating Late 2018 release
ROCLATAN

- What do we think?
  - Side effects- same as Rhopressa
  - Place in therapy?
  - Clinical impressions

- Cost concerns

COMBINATION DRUGS

- Cosopt – timolol-dorzolamide
- Timolol ½%, Dorzolamide 2%
- This drop works better than either timolol or dorzolamide does on their own
- Cosopt is not as effective as if you were using both timolol and dorzolamide
- Same side effects as beta-blockers and CAIs
- Capice? Kapeesh?
COMBIGAN™
(BRIMONIDINE TARTRATE/TIMOLOL MALEATE OPTHALMIC SOLUTION) 0.2%/0.5%

- Fixed combination of brimonidine and timolol
  - Alpha-agonist brimonidine
  - Beta-blocker timolol
- Preserved with 0.005% benzalkonium chloride (BAK)
  - Generic timolol is preserved with 0.01%
- Complementary mechanisms of action

BRIMONIDINE/TIMOLOL COMBINATION HAS DUAL MECHANISM OF ACTION

<table>
<thead>
<tr>
<th>No Outflow Effect</th>
<th>Timolol</th>
<th>↓ Aqueous Production</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inflow and Outflow Effect</td>
<td>Brimonidine</td>
<td>↓ Aqueous Production</td>
</tr>
<tr>
<td></td>
<td></td>
<td>↑ Uveoscleral Outflow</td>
</tr>
</tbody>
</table>

**MEAN IOP—10 AM**

- Brimonidine/timolol fixed combination

> **Mean IOP (mm Hg) at peak**

*P < .001 vs brimonidine or timolol

**Statistical significance does not necessarily correlate to clinical significance.**

**Brimonidine and timolol monotherapies are approved for first line therapy.**


*Data on file, Allergan, Inc.*

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**DIURNAL MEAN IOP AT MONTH 12**

*P < .001 vs timolol

**P < .001 vs brimonidine

**Statistical significance does not necessarily correlate to clinical significance.**

TREATMENT-RELATED ADVERSE EVENTS

Conjunctival hyperemia  Ocular stinging  Eye pruritus  Allergic conjunctivitis  Conjunctival follicles  Oral dryness

***Brimonidine and timolol monotherapies are approved for first line therapy.

FIXED COMBINATION VS CONCOMITANT THERAPY: EQUIVALENT MEAN IOP

NEXT STEP FROM A BETA-BLOCKER

- Additional IOP lowering achieved with fixed combination after beta-blocker run-in

![Graph showing mean change from beta-blocker-treated baseline IOP (mm Hg)]

- Mean change from beta-blocker-treated baseline IOP (mm Hg):
  - Week 0: Hour 0, Hour 2
  - Week 2
  - Week 6
  - Week 12

Fixed-combination brimonidine/timolol BID (n = 121)

Baseline mean IOP = 25.0 mm Hg (hour 0); 22.7 mm Hg (hour 2)


COMBIGAN™ AND COSOPT®

- Randomized, investigator-masked, 3-month, parallel comparison
- Pooled data from 2 studies at 10 sites with identical protocols (Canada)
- Patients with OAG/OHT requiring additional IOP lowering
- Two subgroups
  - Monotherapy: COMBIGAN™ (brimonidine tartrate/timolol maleate ophthalmic solution) 0.2%/0.5% (n = 54) and Cosopt® (dorzolamide hydrochloride-timolol maleate ophthalmic solution) (n = 47)
  - Adjunctive: COMBIGAN™ added to PGA (n = 37) and Cosopt® added to PGA (n = 42)
- IOP 2 hours after morning dose
  - Visits at baseline, 1 month, and 3 months

- PGA = prostaglandin analogue
COMBIGAN™ AND COSOPT® AS MONOTHERAPY: MEAN IOP

Mean IOP reductions from baseline at month 3 were 7.7 mm Hg with COMBIGAN™ and 6.7 mm Hg with Cosopt® (*P = .040).

COMBIGAN™ IN ADJUNCTIVE THERAPY WITH A PGA: MEAN IOP

Mean IOP reductions from baseline at month 3 were 6.9 mm Hg (*P < .0001 vs baseline).

1Nixon and Hollander. AAO, 2007. 2Data on file, Allergan, Inc.
**COMBIGAN™ AND COSOPT® TOLERABILITY AND COMFORT**

- **Stinging:**
  - COMBIGAN™: P = .0001
  - Cosopt®: P = .0149

- **Burning:**
  - COMBIGAN™: P = .0047

- **Unusual taste:**
  - COMBIGAN™: P = .0001


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**OCULAR COMFORT: COMBIGAN™ (BRIMONIDINE TARTRATE/TIMOLOL MALEATE OPHTHALMIC SOLUTION) 0.2%/0.5% AND COSOPT® (DORZOLAMIDE HYDROCHLORIDE-TIMOLOL MALEATE OPHTHALMIC SOLUTION)**

**30–40 Seconds After Drop Instillation**

- **Percentage of subjects rating treatment as most comfortable:**
  - COMBIGAN™: 80%

- **Treatments equally comfortable:**
  - COMBIGAN™: 10%
  - Cosopt®: 10%

**OCULAR DISCOMFORT: COMBIGAN™ (BRIMONIDINE TARTRATE/TIMOLOL MALEATE OPHTHALMIC SOLUTION) 0.2%/0.5% AND COSOPT® (DORZOLAMIDE HYDROCHLORIDE-TIMOLOL MALEATE OPHTHALMIC SOLUTION)**

### Mean Ocular Discomfort Score

**30–40 Seconds After Drop Instillation**

<table>
<thead>
<tr>
<th></th>
<th>COMBIGAN™</th>
<th>Cosopt®</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean ocular discomfort score</td>
<td>0.43</td>
<td>1.97</td>
</tr>
</tbody>
</table>

*P < .0001 vs Cosopt®

n = 30

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**TREATMENT-RELATED ADVERSE EVENTS**

- Oral dryness and adverse events related to conjunctival allergy/inflammation significantly less common with fixed brimonidine/timolol than with brimonidine.

*P ≤ .03 vs brimonidine 0.2% TID

**P ≤ .02 vs timolol 0.5% BID

- Oral dryness
- Conjunctival hyperemia
- Eyelid edema
- Allergic conjunctivitis
- Conjunctival follicles
- Ocular pruritus


**Chan et al. J Ocul Pharmacol Ther. 2007.**
COMBINATION DRUG #3

- Cosopt PF
  - Preservative free
  - Unit dosage vial
  - Able to lower IOP as good as preserved, branded Cosopt
  - BID
  - So??!

COMBINATION DRUG #4

- Simbrinza (Alcon)
  - Brinzolamide 1.0%/Brimonidine 0.2%
  - TID Dosing
  - Approved for adjunctive therapy
  - Adjunctive to what?!
SIMBRINZA

• 5-9 mm Hg IOP reduction

• Baseline IOP – 22 -36mm Hg

• 21- 35% IOP reduction

• TID dosing

SIMBRINZA

• Compared to Azopt head-to–head

• Compared to Brimonidine 0.2% head- to –head

• Statistically superior to either of the components in lowering IOP 2 3 mths

• At all time points
SIMBRINZA – SAFETY DATA

- Side effects are similar to each of the component drugs
- D/C rate – 11%
- 3-5% incidence rate of:
  - Blurred vision
  - Ocular irritation
  - Bad taste
  - Dry mouth
  - Ocular allergy

ONE FINAL WORD ABOUT GLAUCOMA DRUGS

- A lot of money is being spent on delivery systems
- These may be cheaper alternatives
- Optometry cannot sleep on this
BIMATOPROST SR

• Biodegradable sustained-release implant
• Injected intracameraly using single use applicator
• Implant is visible in irido corneal angle
• Could make a big impact on non-compliance issues
• Lowers IOP over a 4-6 month period

BIMATOPROST SR

• Phase 1 data
  • Proved safety and good tolerance
• Phase 2 data
  • 2 weeks
    • IOP 23.8 in Bimatoprost group
    • 24.1 in timolol group
  • At 6 months
    • 20.1 in implant group
    • 19.0 in timolol group
BIMATOPROST SR

- Second study showed IOP decrease of 7.2 - 9.5 mm Hg
- At month 6, 70% of subjects did not require topical IOP gtt
- Biggest side effect is transient hyperemia and FB sensation

- Implications for ODs

NOVEL DRUG DELIVERY SYSTEMS - THE NEXT FRONTIER

- Drug Eluting Punctal Plugs
  - QLT – latanoprost
  - 75% - 80% retention rate
  - Results - 3-4mm drop in IOP

- Ocular Therapeutix – Intracanalicular latanoprost
  - Good sustained release of drug but doesn’t lower IOP as good as topical Xalatan

- SOOOO????
BRIMONIDINE DRUG-ELUTING PLUGS

• Similar technique to inserting collagen lacrimal plugs
• Early studies show better and more sustained IOP release than latanoprost plugs
• Good safety profile
• SOOOO>>>???
ERIC'S 7 SIMPLE RULES FOR TREATMENT

1. Choose 30% IOP decrease as initial target
2. Squash the diurnal curve (Keep IOP peak <18mm)
3. Assess risk factors for progression and rate of progression
   (CT<555, IOP >26, C/D 0.5)

ERIC'S RULES CONT.

4. If you are going to treat; treat aggressively
5. KISS
6. Be mindful of perfusion issues
7. Above all, do no harm
IOP LOWERING WITH MONOTHERAPY IS IDEAL

- Initial therapy with PGA can provide > 30% IOP lowering
- Monotherapy may reduce the risk of adverse events, drug interactions, and exposure to preservatives
- Monotherapy is convenient, may help patient compliance, and may have lower acquisition cost

PATIENTS ON MORE THAN ONE IOP-LOWERING MEDICATION

Source: Verispan’s PDDA, MAT Nov 2006.
HOWEVER, PATIENTS ON MONOTHERAPY MAY NOT ACHIEVE TARGET IOP

- In a study of ocular hypertension patients (OHTS)\textsuperscript{1}
  - At month 60, 40% required 2 or more medications to reach 20% IOP reduction
- In patients treated with PGAs\textsuperscript{2}
  - Adjunctive medication use was 30.2% with latanoprost, 23.2% with bimatoprost, and 22.5% with travoprost


REGARDING PROSTAGLANDINS:

- Generally the 1\textsuperscript{st} line of treatment
- There are interindividual differences in efficacy
- Are there racial differences?
- If at first one fails; try, try, try again (with another prostaglandin)
- Why wouldn’t you use a prostaglandin 1\textsuperscript{st}?
TREATMENT PARADIGM – STEP 2

• Prostaglandins 1st
• If not successful – try another agent by itself: Brimonidine bid or timolol
• If neither of these get IOP to desired level then add

MANY PATIENTS REQUIRE ADJUNCTIVE THERAPY

• Ocular Hypertension Treatment Study (OHTS)\(^1\)
  • 817 patients with OHT; target pressure reduction = 20%
  • At month-60 visit, 39.7% of patients in the medical treatment group required 2 or more medications to reach the target IOP
• Collaborative Initial Glaucoma Treatment Study (CIGTS)\(^2\)
  • 307 newly diagnosed patients with mild to advanced glaucoma; aggressive target pressures set per formula
  • After first 2 years, >75% of patients required 2 or more medications to reach target IOP
• Even patients on the most powerful IOP-lowering medications often require adjunctive therapy\(^3\)

CONSIDER MECHANISM OF ACTION (MOA) WHEN ADDING MEDICATIONS

- Best chance of additivity by combining medications with different mechanisms
- Hypotensive lipids lower IOP by increasing aqueous outflow (uveoscleral/trabecular)
- Complement a hypotensive lipid by adding a drug that inhibits aqueous production
  - Brimonidine
  - CAI
  - Beta-blocker

TREATMENT PARADIGM, PART III

- The Paradigm Is Changing
- Be Creative
- Understand your options
- Understand what you are trying to Achieve
- VF Preservation and Neuroretinal Rim Preservation
- Be aware of side effects
TREATMENT PARADIGM, PART IV

• If on 2 meds and target IOP not met…

• What is maximum medical therapy nowadays?

• SLT and trabeculectomy should not be considered weapons of last choice or last chance