Adjunctive Therapy in Glaucoma
What Do You Do When The First Drop Is Not Enough?

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September 25, 2011

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What do you do when the first drop isn’t enough?

- Confirm compliance
- Factors to consider:
  - Cost/ patient finances
  - Patient mental capacity
  - Patient confusion
    ➢ Written instructions
  - Patient education

Compliance in Glaucoma

- Noncompliance as high as 59%
- Forgetfulness the most common reason
- High IOP can be a predictor of noncompliance or indicate a non-responder
- Compliance increases before an office visit
- IOP measurements may be misleading and not reflect variation when medication was omitted

Compliance in Glaucoma Patients

Recommended strategies for increasing patient knowledge and understanding

- Elicit further questions and/or concerns patient has with treatment.
- Utilize staff assistance in patient education.
- Have patient show you how they use their eye drops.
- Provide written instructions.

Compliance Test

- Verify IOP on follow up visit
- “If your IOP is still up, we will need to consider surgery (or laser treatment) as the next option”
Confirm True Effect of Medication
- Evaluate multiple pre and post medication IOP measurements
- Consider unilateral trials
- Consider response vs. CCT
- Watch for diurnal shift
  - RTC same time of day as initiation of drug

Diurnal IOP Fluctuation & Visual Field Loss
- 64 patients: IOP 5x/day
- VF progression tracked x 8 years
- Diurnal IOP fluctuation positively correlated with visual field loss

Asrani et. al. 2000, Large diurnal fluctuations in intraocular pressure are an independent risk factor in patients with glaucoma, J. Glaucoma, 9, 134-142

Travoprost: Diurnal control over 24 hours
Is There a Difference in Prostaglandin Diurnal Curve Control?
- Difference in 24 hour control?
- Longer term control?

When should additional medications be used?
- Increase therapy if:
  - Progressive VF loss
  - Progressive disc damage
  - TARGET IOP NOT MAINTAINED

Early Manifest Glaucoma Trial
- For every 1 mm IOP lowered, risk of progression decreases by 10%
- Relative risk of progression decreased by 50% with treatment
- No significant adverse effects

Drug Principles
- Higher the initial IOP, the greater the decrease in IOP (mm) for a given medication
- The first drug used will probably provide the greatest change in pressure (mm Hg)
Options for Adjunctive Therapy

- Prostaglandin first
- Beta blocker?
- Alphagan?
- Topical CAI?

Dosage Schedule/IOP Response

- Nonselective beta blockers qd (am) -25%
  • Timoptic, Betimol, Betagan, Ocupress
- Betoptic-S bid (but safer) -20%
- Topical CAI’s bid-tid -20%
  • Azopt, Trusopt
- Alpha agonists bid-tid -23%
  • Alphagan
- Prostaglandins qd (pm) -30%
  • Travatan, Xalatan, Lumigan

The Washout Effect

Beta Blockers as Adjunctive Therapy to a Prostaglandin Analogue

Latanoprost and Timolol Combination Therapy vs Monotherapy

- To compare fixed combination of latanoprost/timolol qd vs. latanoprost qd and timolol bid
- Results: 6 months
  • Timolol 23.4 +/- 5.4 mm BL 23.7 mm
  • Latanoprost 20.8 +/- 4.6 mm BL 22.9 mm
  • Combination 19.9 +/- 3.4 mm (P<.01) BL 23.1

Beta-blockers: Efficacy of Combination vs. Monotherapy

Alpha-2 Agonists as Adjunctive Therapy: Alphagan-P

- Prospective, multicenter trial compared the efficacy of Alphagan-P/Lumigan and timolol GFS/Xalatan in 28 patients with glaucoma or ocular hypertension
- Mean IOP reduction at 3 mo. (10 AM):
  • Alphagan-P/Lumigan: 8.5 mm Hg
  • Timolol GFS/Xalatan: 7.7 mm Hg
  (p = NS)
**Topical CAIs: Adjunctive Therapy**
- IOP-lowering effect of Trusopt and Xalatan studied in 30 patients with glaucoma
- After 3 weeks, Trusopt tid resulted in an additional 2.8 mm Hg IOP reduction in Xalatan-treated patients


**Adjunctive Therapy With Topical CAIs: Effect on Mean IOP**

**Topical CAIs: Adjunctive Therapy**
- 32 POAG patients subdivided into 2 treatment groups for 14 days
  - **Group A**: Initial treatment with dorzolamide bid for 7 days, latanoprost qhs added
  - **Group B**: Initial treatment with latanoprost qhs for 7 days, dorzolamide bid added

**Topical CAIs: Adjunctive Therapy Additive IOP Lowering Effect of Various Medications With Xalatan**
- IOP-lowering effects of β-blockers, Alphagan, and Trusopt were compared in 73 patients (73 eyes) inadequately controlled on Xalatan alone
- After 1 year, adjunctive Trusopt (bid or tid) resulted in 3.9 mm additional IOP reduction vs. 2.5 mm reduction for β-blockers and 2.0 mm for Alphagan.


**Agents Used in Combination with Prostaglandins: Effect on IOP**

**Concomitant administration of travoprost and brinzolamide vs. fixed latanoprost/timolol combined therapy**
- 44 eyes of 44 patients treated with:
  - Xalacom (Xalatan/timolol) n=22 LT group
  - Travatan qd/Azopt bid n=22 TB group
  - IOP measured 9:00am, 12:00, 4:00pm
  - Baseline, 2 weeks, 1 month, 3 months
Results
- No significant difference at 12pm and 4pm
- Mean reduction in IOP
  - TB Group: 29.1 +/- 6.0%
  - LT Group: 25.8 +/- 8.8%
- TB Group also had greater percentage of responders (IOP reduction >30%)

Topical CAIs: Formulations and pH
- To remain in solution, dorzolamide must be formulated at a non-physiologic pH
- Brinzolamide is formulated as a micro-fine suspension at a pH equivalent to human tears

Effect of Comfort on Compliance
Additivity of Bimatoprost or Travoprost to Latanoprost in Glaucomatous Monkey Eyes
- Xalatan with Travatan added
  - Travatan with Xalatan added
- Xalatan with Lumigan added
  - Lumigan with Xalatan added
- Xalatan with Xalatan added

IOP measurements (x 6)
- Day 1 (baseline)
- Days 6 & 7 (one week of monotherapy)
- Days 13 & 14 (1 week of combo therapy)

Monotherapy IOP Reduction
- Travatan    7.0mm    20%
- Xalatan     7.5mm    22%
- Lumigan     6.5mm    18%
- All statistically equivalent

Travatan Added to Xalatan
Lumigan Added to Xalatan
Is Addition of a Third or Fourth Antiglaucoma Med. helpful?

- To study the IOP lowering effect of adding a 3rd or 4th glaucoma medication
- Efficacy Success: 20% reduction of IOP

3rd medication:  4th medication:
- 2 mos. 48%  59%
- 6 mos. 47%  45%
- 1 yr. 41%  55%

Efficacy/Safety Cumulative Success

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<th>3rd med.</th>
<th>4th med.</th>
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<tr>
<td>6 mos.</td>
<td>27%</td>
<td>14%</td>
</tr>
<tr>
<td>1 yr.</td>
<td>31%</td>
<td>14%</td>
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Conclusion: Addition of a 3rd or 4th med. produces a clinically significant reduction in IOP in 40%-60% of patients at any single time point. However, the cumulative probability of success is relatively poor at 6 and 12 months.

Use of Combination Agents

- Cosopt
  - Timolol 0.5%/ dorzolamide
- Pro
  - Effective
  - Convenient
- Con
  - More timolol than necessary or desired
    - 2nd dose no more effective and may increase side effects
  - Dorzolamide stings
  - Expensive

ALT/SLT Considerations

- Pro
  - Safe: minimal risks
  - No medical side effects
  - Relatively effective
  - No compliance issues
  - May be less expensive to patient
  - Convenience
- **Con**
  - Initial cost
  - Duration of effect

**When Should Laser Treatment be Considered?**
- POAG, Pigmentary, PXE
  - Avoid in other types
- Consider after two medications
- Consider to further lower IOP (EMGT)
- Consider prior to surgery
  - When likely to be effective enough to avoid, delay surgery

**What Have We Learned?**
- Prostaglandins first
  - Remember compliance issues
- CAI, alpha agonist or beta blocker
- Be aggressive with damage/progression
  - Consider risks vs. benefits
  - 1mm decrease= 10% decrease risk of progression
- Monitor carefully for change