Glaucoma medical therapy

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Basics: *Definition of POAG.*

- **Chronic progressive anterior optic neuropathy:**
  - Not associated to other ocular pathology.
  - Intra-ocular pressure (IOP) is a primary risk factor.
    - Primary target for therapy.
- Characteristic optic nerve and field changes.
- Bilateral, although often asymmetric.
Basics: *Principles of Therapy.*

- Main goal is to prevent loss of function.
- Ways:
  - In 2007: lowering the IOP.
    - Increase in outflow facility.
    - Decrease in inflow.
  - Future: decrease optic nerve susceptibility.
    - Prevention of secondary death loss. Neuroprotection?
      - Memantine, phase 3.
      - Aminoguanidine.
      - T-cell vaccination with antigens that cross-react with optic nerve and retinal antigens.¹

Principles of Therapy: IOP Level.

- Optic nerve status.
  - Stereo photos, Optic Nerve Imaging.
- Visual field.
  - baseline.
  - progression.
- CCT. 520 & 550.
- Medical History.
  - DM ? (OHTS), HBP, Vascular insufficiency.
- Family History.
**Principles of Therapy: IOP Level.**

- Targets are lower in 2008.
  - 14 or less in severe disease. (11.8 or less?).
  - 35 % lower from baseline in mild-moderate.
    - CIGTS. OPH Vol. 108 Nov 2001
  - 35% lower from baseline in NTG.
Principles of Therapy: General.

- Thorough medical history.
  - possible side effects and drug interactions.
- Lacrimac sac occlusion or gentle lid closure.
- Therapeutic trial.
  - 3-6 weeks period.
**Principles of Therapy: General-II**

- Medical treatment remains first line of defense.
  - Prostaglandins are still “in”.
  - Oral CAI is definitely “passé”.
- Regardless.
  - Know your choices.
  - Remain suspicious of anybody.
  - Therapeutic Trial.

Rx companies, lawyers and used cars salesmen.
Medical Therapy.

- Decrease inflow.
  - Beta blockers.
  - Alpha 2 adrenergics.
  - Topical Carbonic Anhydrase Inhibitors (CAIs).

- Increase outflow
  - Cholinergics.
  - Alpha 1 Adrenergics.
  - Alpha 2 adrenergics.
  - Prostaglandins.

- Future products.
Evolution.

- 1875. Pilocarpine.
- 1925. Epinephrine.
- 1950’s. E-pilo & Diamox.
- 1980’s, other beta-blockers: Betagan, Betoptic, Optipranolol, Cartelol.
- 1996. Latanaprost, Brimonidine.
Beta Blockers.

- Mechanism:
  - suppression of inflow.
  - direct action on the ciliary processes.
  - blockade of “resting tone” through beta-2 receptors.
  - inhibition of the c-AMP.

- no effect on blood-aqueous barrier.

- additive to cholinergics, α-2 adrenergics, systemic or topical CAIs, and prostaglandins.
Beta Blockers: “Cardio-selective”

- Betaxolol (Betoptic 0.25%, 0.5%).
  - less pulmonary effects
    - (almost no beta-2 blockade).
  - probably less cardiovascular changes.
    - less affinity for beta-1 receptors than non-specific.
    - Greater binding to plasma protein.
      - probably less systemic side effects.
  - average drop in IOP: 3-5 mm Hg. (hopefully)
  - dosage 0.5% or 0.25% (S) bid.
**Beta Blockers:** Non selective group.

- **Respiratory side effects.**
  - Asthma.
  - COPD.
- **Negative chronotropic and inotropic effects.**
  - Bradycardia, heart block, arrest.
  - CHF.
- **Average IOP drop: 5-7 mm Hg.**
  - Much less if patient is on systemic beta-blockers.
Non selective group, other side effects.

- Mental changes: depression, anxiety.
- Impotence, decrease libido.
- Maculopapular rash, alopecia.
- GIT changes.
- Exacerbation of Myasthenia Gravis.
- Downplay hypoglycemic symptoms.
- Increase TG, decrease HDL.
Non selective agents.

- **Timolol (0.25%, 0.5%).**
  - best known, peak 2 hr. dosage q 12 hrs.
    - Most important, AM dose.
  - short term escape, long term drift.
  - ocular side effects.
    - Superficial punctate keratitis (SPK).
    - redness, corneal anesthesia, dry eye.
    - allergy.
- Gel, XE q 24 hr. am.
- Still in the game, specially in secondary glaucoma.
Non selective agents, cont.

- Levobunolol (Betagan 0.25%, 0.5%) bid.
  - may be used q 24 hr. due to active by-products.
    - AM.
  - severe toxic reaction in some patients.
    - lid edema.
    - follicular conjunctivitis.
  - indications, usage and side effects quite similar to timolol.
Non selective agents, cont.

- Metipranolol (Optipranolol 0.3%).
  - q 12 hrs., cheaper.
  - follicular conjunctivitis.
  - corneal anesthesia, SPK.
  - average IOP drop: 4-6 mm Hg.
  - Iritis.
    - Isolated batch UK?
Non selective agents, cont.

- Carteolol (Ocupress 1%).
  - peak 4 hrs, dosage q 12 hrs.
  - some intrinsic sympathomimetic activity.
    - less systemic side effects?
    - less decrease in HDL, less increase in TG than timolol.
  - less irritation.
**Beta Blockers**: Drug interactions.

- Additive to cholinergics, CAIs, alpha-2 adrenergics and prostaglandins.
- Historic value:
  - limited additive effect with Propine/Eppy.
  - may be more if Betoptic is used.
- Systemic.
  - Ca++ channel blockers, heart block.
    - Verapamil (Calan). Nifedipine (Procardia, Adalat).
  - Systemic beta blockers.
    - Limited IOP lowering.
Cholinergics: Mechanism.

- Direct agonists. *Back to the future.*
  - Increase outflow facility by direct stimulation of the cholinergic receptors leading to ciliary muscle contraction.
    - Decrease uveoscleral outflow.
  - Pilocarpine (true direct).
    - Solution, gel.
    - Brought to life just by economics.
  - Carbachol (combined).
    - Out of the shelf.
Cholinergics: Mechanism.

- **Indirect agonists.**
  - Historic & Academic curiosity.
  - Increase outflow by inhibition of acetylcholinesterase.
  - “Reversible” antidote: atropine.
    - Physostigmine and Neostigmine (congestion).
  - “Irreversible” antidote: protopam.
    - Ecothiophate Iodide.
    - Demecarium Phosphate.
Cholinergics: Direct agents.

- Pilocarpine 0.5%-10%.
  - onset 15 mins, peak 2 hr, dosage q 6 hrs.
  - steps: 1, 2 and 4% (6% rarely of help).
  - miosis, myopia, pain, blurred vision.
  - cataracts, R/D?
  - GIT symptoms, > 4%.
  - increase pulmonary secretions (careful in B.Asthma).
Cholinergics: Direct Agents.

- **Carbachol 0.75%, 1.5% & 3%**.
  - q 8 hrs, more ciliary pain.
  - less corneal penetration, try timolol first AM.
  - **No longer available**.

- **Delivery systems for pilocarpine**.
  - Pilopine gel 4% hs, roughly equal to pilo 1-2%.
    - follicular conjunctivitis.
    - **Main use: OR**.
      - Pupil down to 1-2 mm next day, decrease IOP spikes.
  - **Ocusert. 20-40**, change every 5-7 days.
    - Pigmentary Glaucoma
Cholinergics: Indirect agents.

- **Ecothiophate Iodide. (Phospholine I).**
  - 0.03, 0.06, 0.125 & 0.25%.
  - optimal 0.06 or 0.125% qd or q 12 hr.+
  - ocular side effects.
    - worse than direct agonists.
    - cataracts, R/D.
    - increase pupillary block.
    - breakdown in blood aqueous barrier.
Indirect agents, cont.

*Ecothiophate Iodide. (Phospholine I).*
- Systemic side effects.
  - GIT changes.
  - depletion of red cells and serum cholinesterase.
    - prolong apnea with succinylcholine (GETA).
- Use: aphakes, pseudophakes.
  - Strabismus for high A/C ratio.
- Production stopped 2001.
Adrenergic agonists.

- *Epinephrine & Propine*, mechanism.
  - transient initial decrease in aqueous production.
  - increase in outflow.
    - initial increase in TM outflow.
    - sustained late increase in uveoscleral outflow?
  - additive to cholinergics and CAIs.
    - less to beta-blockers and alpha 2 agonists.
Adrenergic agonists: Agents.

- **Epinephrine 0.5, 1 & 2%**.
  - optimal 1% bid.
  - 1% HCL or borate roughly has the same free base than 2% bitartrate.
- **Ocular side effects**.
  - redness, pigmentation, follicular conjunctivitis.
  - madarosis, stenosis of punctum.
  - pain.
Adrenergic agonists: Agents.

- **Epinephrine 0.5, 1 & 2%**.
  - Ocular side effects.
    - mydriasis, increase relative pupillary block.
    - CME, aphakia and pseudoaphakia (20-30%).
    - decrease endothelial cell count.
    - ocular hypoxia?, avoid in NTG.
  - Systemic cardiovascular (HBP & HR).
  - Headaches, anxiety.
Adrenergic agonists: Agents.

- Dipivefrin (Propine 0.1%).
  - dosage q. 12 hrs.
  - two pivalic acids added to epinephrine.
    - more lipophilic, 17x corneal penetration.
  - pro-drug, biotransformation by corneal esterase before being effective.
  - much less systemic side effects.
  - similar ocular side effects (but no SCL staining).
Alpha adrenergic agonists

- Apraclonidine (Iopidine 0.5, 1%).
  - alpha 2 pre-synaptic agonist.
    - Inhibition of adenyl cyclase, ↓ cAMP.
      - ↓ release of norepinephrine; ↓ beta stimulation.
      - decrease inflow by vasoconstriction of ciliary processes.
  - poor penetration of CNS.
    - no significant hypotension (alpha stimulation in the brainstem reduced sympathetic tone).
Alpha adrenergic agonists

- Iopidine 0.5%.
  - chronic use q 8 hrs, very expensive.
  - works fine in ant. segment laser surgery.
    - As good as the 1% unit dose and cheaper for the surgeon.
  - additive to miotics, beta-blockers and CAIs.
    - limited effect if added to two inflow suppressors.
    - poor choice if added to other adrenergic (vasoconstrictor).
  - average drop 2-4 mm Hg if added to multiple therapy.
Alpha adrenergic agonists

- Iopidine 0.5%.
  - tachyphylaxis.
  - hyperemia, follicular conjunctivitis.
  - dry mouth & nose.
  - sedation.
  - impotence?
Alpha adrenergic agonists

- Iopidine 1%.
  - One hour pre and immediately post laser decrease IOP peak after anterior segment laser surgery. 0.5% works just as fine as it is cheaper.
  - Residual alpha-1 effect.
    - mydriasis.
      - potential increase in pupillary block.
      - add pilocar, for LPI.
    - blanching, lid elevation.
  - Postural hypotension, palpitation, bradycardia.
Alpha adrenergic agonists

- Brimonidine tartrate (Alphagan 0.2%).
  - 32 x alpha-2 selectivity.
    - less tachyphylaxis.
    - less hyperemia, vasoconstriction. (α-1).
    - less follicular conjunctivitis, less oxidative liable.
    - decrease inflow and increase uveoscleral outflow.
- dosage q 8-12 hrs, average drop 4-6 mm Hg.
- watch for contact dermatitis after several months.
- additive to beta-blockers, CAIs, prostaglandins and miotics.
Alpha adrenergic agonists

- Brimonidine tartrate (Alphagan 0.2%).
  - Peak IOP ↓ (2hrs after the morning dose).
    - similar to timolol.
  - Trough IOP ↓ (12 hrs after the evening dose).
    - similar to betaxolol suspension.
  - Decrease in systolic BP.
    - Syncope.
  - No pulmonary effects.
  - Works in prophylaxis of IOP spikes for anterior segment laser surgery, if patient does not use it chronically.
Patent extension or less allergy?

- Alphagan-P. (first 0.15%, now 0.1%)
  - Alphagan with the preservative of Refresh Tears, lower [ ].
  - Purite
- Same dosage, effectiveness & side effects.
- Less allergy but:
  - More money.
Brimonidine Tartrate (Alphagan 0.2%)

- Potential neuroprotective role.
  - Decrease in secondary death after injury.
- In vitro models.
  - Crush injury of rat optic nerve.
  - Phototoxicity on rabbit retina.
  - Retinal ischemia, rat eye.
Carbonic anhydrase inhibitors.

- **Mechanism (systemic).**
  - decrease inflow by inhibition of carbonic anhydrase (type II) in the ciliary processes.
  - metabolic acidosis, not essential but helps.
    - further IOP reduction.
    - increase blood flow to the optic nerve.
    - diuretic effect limited and non-contributory.
  - additive to all other glaucoma medications.
**CAIs: Systemic**

- Electrolytic imbalance.
  - Severe loss of K+, specially if combined with diuretics (lasix!).
  - Interaction with digoxin.
- Kidney stones.
- Blood cell dyscrasias.
- Severe allergic reactions.
- Malaise, anorexia, weight loss, impotence.
CAIs: Systemic

- **Indications.**
  - Acute elevations of IOP.
    - Angle closure.
    - Post-op spikes.
    - Secondary Glaucomas.
- **Acetazolamide (Diamox).**
  - 250 mg po tid or qid. 500 mg seq. Bid.
- **Methazolamide (Neptazane).**
  - 50 mg po bid.
  - Weaker than Diamox.
**CAIs: Topical.**

- **Dorsolamide (Trusopt 2%).**
  - peak 2 hrs, dosage q 8 hrs, ↓IOP 15-20%
  - additive to all other glaucoma meds.
    - Twice a day if used with beta-blockers.
    - And practically with most other meds.

- **Systemic side effects: minimal.**
  - Blood dyscrasias rare but possible.
    - Document “non allergic to sulfa”.

- **Ocular: discomfort, follicular conjunctivitis.**
  - Careful if cornea’s health is a concern (guttata).
CAIs: Topical.

- Brinzolamide (Asopt 1%).
  - Suspension.
    - IOP drop and dosage equal to Dorsolamide.
    - Less irritation, no cross-reaction.
    - Blurred vision.
    - Slightly less expensive.
  - Otherwise similar ocular and potential systemic side effects.
Combinations I.

- Cosopt.
  - Timolol 0.5% + Dorsolamide 2% bid.
  - IOP drop and side effects similar to both drugs added.
  - Avoid combining it with Diamox, no further decrease of IOP is expected and the cornea may suffer.
  - Check for beta-blocker contraindications.
  - Cosopt + PGF is MMT in 2007.
Combinations II.

- Combigan.
  - Timolol 0.5%+ Brimonidine 0.2%. (about 3 mm more than timolol 0.5%)
    - Dosage: bid.
    - Less allergy than Brimonidine alone?
      - Timolol may block decrease cell volume of conj cells produced by Alphagan, this plus vasoconstriction produced by timolol may reduced potential exposure to allergens?
Combinations down the corner

- Available outside US.
  - Timolol + Travatan.
    - Extravan. (yes AM!) 2 mm more than either product alone.
  - Xalacon. (Xalcom)
    - Only in Europe (AM!). Less than 2 mm more.
Prostaglandins: *The PGF family.*

- NSAIA blocks hypotensive response to:
  - Epinephrine.
  - Apraclonidine.
  - ALT (early effect).
- ∴ Prostaglandins affect IOP.
  - Somewhat overrated.
Prostaglandins: The PGF family.

- **Mechanism:**
  - increase uveoscleral outflow.
    - Ciliary body relaxation vs decrease in extracellular matrix.
      - Greater effect with use?
  - antagonized by miotics?
    - Additive effect 10-14%. (two small studies)

- **Side effects.**
  - hyperemia.
  - pigmentation of the iris.
  - breakdown blood-aqueous barrier?
Prostaglandins: *Agents*.

- **Isopropyl esters of PGF$_{2\alpha}$**.
  - Prodrugs, hydrolyzed by corneal esterases.
- **Phenyl substitute analogs**.
  - Increase affinity toward FP receptors.
  - Less “Prostaglandins’ like side effects”
  - Latanaprost and the gang.
- **Other choices (poor)**:
  - **Isopropyl ethyls of PGF$_{2\alpha}$**.
    - Rescula.
Prostaglandins: *Agents*.

- Latanaprost (Xalatan 0.005%).
  - 25-35 % IOP reduction, POAG.
    - Avoid it on secondary glaucoma.
      - Especially if inflammation is present or suspected.
  - dosage q 24 hrs (evening).
  - additive to all glaucoma meds,
    - Limited additive effect expected with miotics.
  - main side effects:
    - iris hyperpigmentation (green, yellow).
Prostaglandins: *Agents*.

- Latanaprost (Xalatan 0.005%).
  - Other side effects.
    - Price (only systemic side effect expected).
    - Hyperemia.
    - Pain.
    - Iritis.
    - Hypertrichosis.
    - Changes eyelid pigmentation.
    - CME in pseudophakia/aphakia. < 1%?
      - Varies from the source of the study.
    - Contraindicated in pregnancy.

Contraindicated in pregnancy.
Prostaglandins: Agents.

- **Rescula.**
  - Widespread use in Japan.
  - IOP drop 15-20%, (closer to 10-15%).
  - Similar in side effects to Xalatan, but somewhat milder.
  - New comers are more effective.
New kids on the block

- Travatan.
  - Travaprost 0.004%.
  - Prostaglandin derivative.
    - Alcon settle the patent war for royalties with Pfizer.

- Lumigan.
  - Bimatoprost 0.03%.
  - Prostamide?
    - Just a prostaglandin fighting a patent.
Travatan.

- Synthetic PGF$_2$ analog.
- Agonist activity at the FP receptor.
- Increase uveoscleral outflow.
- 28% drop in IOP (HS.).
  - May be more effective on blacks than Xalatan.
    - Approved with that language by the FDA, less than 2 mm Hg difference with Xalatan.
- Almost identical side effects.
  - Very red.
  - $55-75 (2.5 ml)$
Lumigan.

- Prostamide?.
  - Synthetic derived from anandamide an endogenous membrane lipid.
  - Does not stimulate any known prostaglandin receptor ??
- 35% drop IOP (HS.).
- Similar side effects.
  - Less iris hyperpigmentation.
  - Red eye, sunken eyes.
  - Price $55-75?, 5ml > $120
Summer of 2008, 2012 never?

- Betaxon.
  - Levobetaxolol 0.5%
  - Suspension.
- As good as timolol without its side effects?
- Other lipids.
- Memantine.
- Unconventional Rx.
  - ginkgo biloba
Summer of 200x: *Betaxon.*

- Almost 100% S-isomer of betaxolol.
  - Same mechanism of action.
  - Same precautions.
- Cardioselective, no intrinsic sympathomimetic activity.
- > IOP reduction?
  - 16-21% trough, (12 hrs), dosage bid.
  - 20-23% peak (2 hrs).
2008+

- Ethacrynic acid revisited.
  - Modified the TM cytoskeleton.
  - Oral forms may do the job.
    - Avoid A/C injections every few weeks-months.
- Other lipids-lowering IOP (PGF related).
- Neuroprotection, yes it may be final answer.
Conclusion: Steps.

Prostaglandins.
Excellent initial response.
Cost, long term effect?

Beta-blockers.
Selective vs Non-Selective

Alpha adrenergic
Acute: Iopidine.
Chronic: Alphagan

Topical CAIs
If not allergic to sulfa.
Consistent
3-4 mm Hg drop.

Laser Trabeculoplasty
ALT vs SLT

Miotics?
Main advantage in chronic therapy:
Cost

Surgery
5 FU or MMC