Management of Glaucoma- A-Z

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Disclosures

- Speakers bureau Sanofi- Genzyme and Allergan

Outline

- Glaucoma drugs
  - Mechanism of action
  - Dosage considerations
  - Side effects
  - Ocular and systemic considerations
- Combination topical medications and considerations
- Neuroprotection and future medications
- Side effects of chronic medical use and preservatives
- Acute IOP spike management in office

Outline

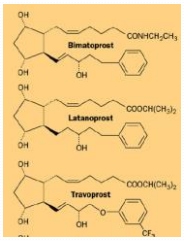
- Possible course of first line of therapy and alternative plans when medications do not work.
- Decreasing pressure in office when intraocular pressure is elevated to unsafe levels.
- Case reports

Prostaglandin analog

- Prostaglandin (PG) analogs, originally introduced for glaucoma therapy in the United States with latanoprost in 1996
- Most effective agents in lowering IOP
- Most commonly used

Various prostaglandin analogs

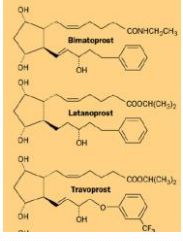
- latanoprost (formerly XALATAN 0.005%, Pfizer, New York, NY)
- travoprost (TRAVATAN Z 0.004%, Alcon, Fort Worth, Tex.)
- bimatoprost (LUMIGAN 0.03%, Allergan, Irvine, Calif.)
- Tafluprost (ZIOPTAN, Merck USA)



Prostaglandin analogs (PGs)

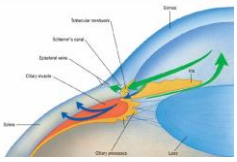
- All PGs have similar structure
- They are prodrugs of Prostaglandin $F_{2\alpha}$
- Converted by corneal enzymes into its active form
- Activates the $F_{2\alpha}$ prostaglandin receptors on ciliary body

- Bimatoprost described as prostamide (nitrogen attached to carbonyl group)



Mechanism of action

- Increases outflow through uveoscleral pathway.
- Does not reduce aqueous production
- Mechanism not fully understood



Mechanism of action cont…

- Two theories
1. Relaxation of ciliary muscle
2. Dilated spaces between cliliary muscle bundles

Relaxation of ciliary muscle- theory

- Supported by experiments with pilocarpine pretreatment experiments in monkeys
  - Human experiments no effect
- Increase in ciliary body thickness when treated with latanoprost

Dilated spaces between cliliary muscle bundles- theory

- PG induced stimulation of collagenase and other matrix metalloprotenases
- Still being investigated.

Contraindications

- Allergic to this drug
- Pregnant or nursing caution
- Pediatric – less effective
- Unclear PGs and ocular inflammation

PGs and inflammation

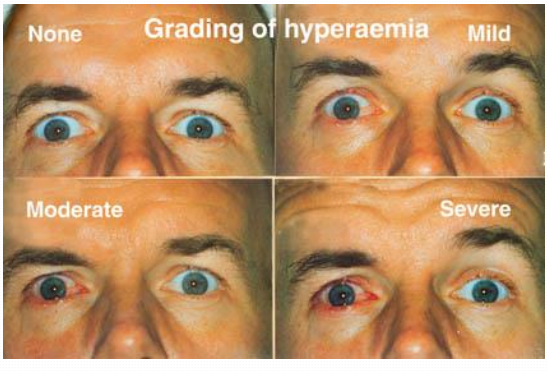
- Not first choice
- Some reports : association of PGs (latanoprost) and cystoid macular edema
- Caution: PGs CME, iritis or hepes simplex keratitis, or immediate post-op
- Don't use- cases with complicated surgery, CME or risk of CME, torn posterior capsules.

Treatment

- Once daily evening
- Helps prevent morning spike in pressure
- Should not be utilized more than once daily
  - Twice daily less effective than once daily

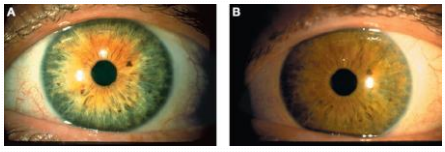
Side effects

- Conjunctival hyperemia
- Iris color change
- Eyelash changes
- Skin pigmentation
- Deepening of upper eye lid sulcus (DUES)



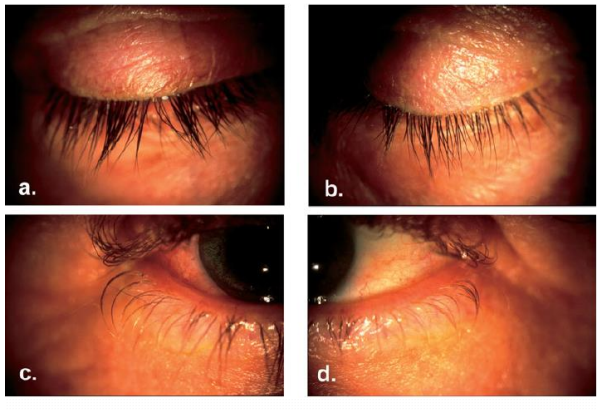
Iris color change

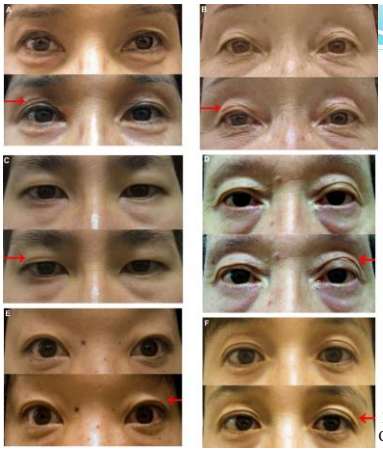
- Well documented side effect
- Overall incidence up to 30-40 %
- Only half the number of patients notice the change
- Increase in melanin content not total number of melanocytes



Eyelash and adnexa changes

- Increase length, number and thickness of eyelashes
- Increase pigmentation of eyelashes
- Eye last bristle
- Cosmetic use Latisse – Bimatoprost
- Skin pigment around eye also increases – wipe off excess decreases the side effect.





Maruyama et al., Clinical Ophthalmology 2013:7 1441–1446

Uveitis and PGs

- Anecdotal and retrospective studies show possible association between the two.
- No clear causal relationship

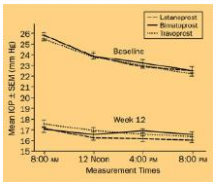
Packer M, Fine IH, Hoffman RS. Bilateral nongranulomatous anterior uveitis associated with bimatoprost. J Cataract Refract Surg. 2003;29:2242–2243.
Parentin F. Granulomatous anterior uveitis associated with bimatoprost: a case report. Ocul Immunol Inflamm. 2003;11:67–71.
Suominen S, Valimaki J. Bilateral anterior uveitis associated with travoprost. Acta Ophthalmol. 2006;84:275–276.
Kumarasamy M, Desai SP. Anterior uveitis is associated with travoprost. BMJ. 2004;329:205.

PGs and systemic side effects

- None
- Prostaglandin analog reaches systemic circulation
- Metabolized by liver
- Elimination by kidneys
- Half life 17 minutes in human plasma
- In contrast to timolol no effect on blood pressure

Comparison of PGs

- All are similar
- Effective in all ethnic groups
- PGs better than timolol in African Americans
- No loss of effect over time.



Additivity

- PGs increase outflow
- So adding it with drugs that decrease production of aqueous makes sense

Beta blockers and PGs

- Beta blockers decrease aqueous production
- Adding beta blockers to latanoprost gives additional 14% drop.
- Adding CAI to PGs also decrease IOP by 15 %
- Adding Alpha 2 agonist decrease IOP by 15%

Fixed combination

- Not available in USA

PG analog	Combination Drug	Brand Name	Manufacturer
Latanoprost 0.005%	Timolol 0.5%	Xalacom	Pfizer
Bimatoprost 0.03%	Timolol 0.5%	Ganfort	Allergan
Travoprost 0.004%	Timolol 0.5%	DuoTrav, Extravan	Alcon

So what's the problem where are the combination of PGs?

- FDA insists that combination of drug should produce additional 20% decrease in IOP
- PGs give 32-33% already
- Addition of timolol or any other drug does not produce additional 20% decrease in IOP

Advantages of fixed combination drugs

- More convenient
- Less expensive
- Improved compliance
- For example
- Timolol BID and latanoprost qd
- Or
- Xalacom qd (combination of latanoprost and timolol)

OPEN

Eye (2013) 27, 841–847
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www.nature.com/eye

CLINICAL STUDY

Fixed-combination brinzolamide 1%/brimonidine 0.2% *vs* monotherapy with brinzolamide or brimonidine in patients with open-angle glaucoma or ocular hypertension: results of a pooled analysis of two phase 3 studies

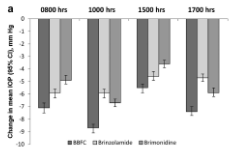
T Realini[1], QH Nguyen[2], G Katz[3] and H DuBiner[4]

SIMBRINZA™ (brinzolamide/brimonidine tartrate ophthalmic suspension) 1%/0.2%

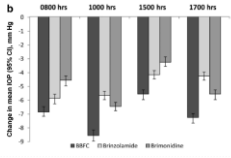
- Sample size
- n= 1350 patients
- Binzolaminde/brimonidine fixed combo n= 437;
- Brinzolamide, n=458;
- Brimonidine n =455.

IOP compared to baseline

6-weeks

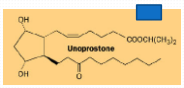


3-months



Unoprostone RESCULA

- Unoprostone (Rescula 0.15%, Novartis Ophthalmics, Basel, Switzerland).



- Initially thought as a prostaglandin
- Now believed to improving trabecular outflow

Side effects similar to prostaglandin

No heart/lung issues

Beta blockers

Historical perspective

- 1964 Propranol was introduced to treat systemic hypertension, angina and cardiac arrhythmias.
- Phillips et al observed a decrease in IOP in glaucoma patients post systemic administration
- Corneal anesthesia a side effect of the drug
- Hence Practolol was developed (no corneal anesthesia) but immunological problems (occulomucocuataneous syndrome).

So the search continued…

- 1970 investigations on timolol
- 1978 timolol maleate obtained FDA approval.

- This is a landmark year as glaucoma management was never the same again…
- Why? Try comparing it to pilocarpine
- Beta blocker soon became primary therapy for glaucoma

General pharmacology

Briefly…

Beta-adrenoreceptors

- Beat -1
  - Receptors found in heart
  - Stimulation causes increase heart rate, cardiac contractility and atrioventricular conduction
- Beta-2
  - Located in bronchial muscle, blood vessels and uterus
  - Stimulation causes dilation of bronchi and blood vessels
- Beta -3
  - Recently identified in mammals
  - Mediation of lipolysis

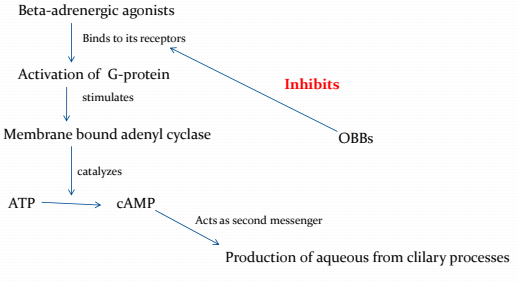
β-adrenoreceptors antagonists

- Topical ocular beta blockers (OBB) are β-adrenoreceptors antagonists
- β-adrenergic antagonists are competitive inhibitors
- Classification
  - Selective (Either beta-1 or beta-2)
  - Non-selective (Both beta-1 and beta-2)
  - **Important: Selectivity is relative at high concentrations selective β-adrenergic antagonists inhibit other beta blockers.**

Mechanism of action

- **Ocular beta blockers (OBBs) act by reduction in aqueous formation**
- No change in outflow facility
- Aqueous formation can decrease as much as 50%
- Exact mechanism still not clear (despite 30 years of use).
- Two hypothesis
  - Classic hypothesis
  - Alternate hypothesis

Classic hypothesis



Evidence against classic hypothesis

- Direct relationship between OBBs and cAMP not supported in all studies (Schmitt 1981).
- IOP can decrease in response to increase in cAMP (Caprioli et al 1984)
- Both dextro –isomer (low affinity) and levo-isomer (high affinity) of timolol decrease IOP. Which gives evidence against competitive inhibition.

Schmitt C, Lotti VJ, DeDouarec JC. Beta-adrenergic blockers: lack of relationship between antagonism of isoproterenol and lowering of intraocular pressure in rabbits.In: Sears ML, ed. New Directions in Ophthalmic Research. New Haven, CT: Yale University Press; 1981:147–162.
Caprioli J, Sears M, Bausher L, et al. Forskolin lowers intraocular pressure by reducing aqueous inflow. Invest Ophthalmol Vis Sci. 1984;25:268–277.

Alternate mechanisms of OBBs

- Clilary process are under continuous tonic stimulation to produce aqueous (mediated by epinephrine).
- Beta- blockers interfere with tonic stimulation

- This is a speculative hypothesis
- No anatomic basis identified yet.

Indications

- Lowering IOP ocular hypertension and open angle glaucoma
- May be used stand alone or in combination with other drugs
- Secondary glaucoma
- Angle closure glaucoma

Contraindications

- Relative or absolute contraindication in patients with
  - Pulmonary disease, bronchial asthma, severe COPD
  - Betaxolol (selective OBB is not contraindicated for above diseases)
- Any patient with sinus bradycardia (less than 60 beats resting), overt congestive heart failure
- Any patient that develops ether heart or lung problems after starting OBBs
- Patient hypersensitivity to drug or any component

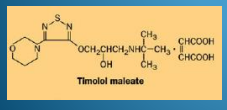
Treatment regimen

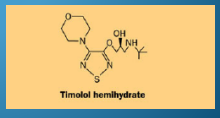
- OBBs used once or twice daily
- Twice daily may lower IOP greater than once daily
- More and more practitioners use qd and increase to bid if needed (to minimize side effects)
- All OBBs twice daily
- Exception
  - Isatalol qam
  - Timoptic XE or GFS (gels) qd
  - Betagan qd

Data from PDR

Drug	Comment	Concentration (%)	Supplied (mL)	Preservative
Timolol	Maleate generic	0.25, 0.5	5, 10, 15	BAK 0.01%
Timoptic	Maleate	0.25, 0.5	5, 10	BAK 0.01%
Timoptic	Ocudose unit dose	0.25, 0.5	0.2	Preservative-free
Betimol	Hemihydrate	0.25, 0.5	5, 10, 15	BAK 0.01%
Istalolol		0.5	5	BAK 0.005%
Timoptic-XE	Gellan gum gel-forming solution	0.25, 0.5	5	Benzododecinium bromide 0.012%
Timolol GFS	Xantham gum	0.25, 0.5	2.5, 5	Benzododecinium bromide 0.012%
Carteolol	Generic	1.0	5, 10, 15	BAK 0.005%
Ocupress	Not available			
Levobunolol	Generic	0.25, 0.5	5, 10, 15	BAK 0.004%
Betagan		0.25, 0.5	2, 5, 10, 15	BAK 0.004%
Metipranolol	Generic	0.3	5, 10	BAK 0.004%
OptiPranolol		0.3	5, 10	BAK 0.004%
Betaxolol				
Betaxolol solution	Not available	0.5		
Betoptic S	Suspension	0.25	2.5, 5, 10, 15	BAK 0.01%

Timolol





Timolol

- Available as timolol maleate or hemihydrate 0.25 and 0.5%
- Commonly used 0.5%
- Non selective beta-adrenergic antagonist
- No corneal anesthesia (like propranolol)
- Greater efficacy than pilocarpine
- Lowers IOP in normals, ocular hypertensive and glaucoma patients

Timolol cont…

- Good alternative to prostaglandins when used appropriately
- Onset of action 30 minutes following instillation
- Peak action 2 hours
- Maximal effect can persist for 12 hours
- IOP lowering persists for 24 hours

AM/PM efficacy

- Timolol AM dose reduces IOP below baseline
- Timolol PM dose does not reduce it below baseline levels.

- This casts doubt on its efficacy on PM dosing.

Short term escape

- Not in all patients
- Efficacy of timolol decreases over time (several weeks)
- Response of beta receptors to constant antagonist
- There may be an up regulation of beta receptors in target tissue

- Important- not in all patients!

Long term drift

- Over months to years
- Control of IOP not as good as once.
- Washing out and re-starting helps restore levels

- Lack of efficacy or poor adherence ??? We don't know for sure

Gels versus drops

- Gels :
- improve bioavailability
- Decreases systemic absorption
- Once a day dose instead of twice a day – compliance /adherence may be better
- Blurs vision if left over in morning
- Timoptic XE preserved with benzododecinium bromide (not BAK)

Timolol hemihydrate

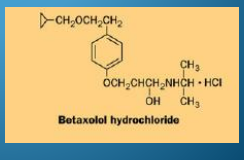
- Same side effects as timolol maleate
- Lowers IOP the same

Istalol

- Timolol maleate 0.5%
- Formulated with potassium sorbate
- Claims to enhance bioavailability **so once daily**.
- Lower BAK concentration
- Most visits IOP difference is within 1.0mmHg between groups 95% CI
- All visits within 1.5mmHg (compared to twice daily)

Mundorf TK, Ogawa T, Naka H, Novack GD, Crockett RS; US Istalol Study Group. A 12-month, multicenter, randomized, double-masked, parallel-group comparison of timolol-LA once daily and timolol maleate ophthalmic solution twice daily in the treatment of adults with glaucoma or ocular hypertension. Clin Ther. 2004;26(4):541–551.

Betaxolol



Betaxolol hydrochloride

- Selective beta blocker
- Initially 0.5% **solution (1985)**
- Later 0.25% suspension of resin coated beads (gradual release) – Betoptic S (Suspension)
- Betaxolol **solution** is no longer available in USA

Betaxolol suspension (Betoptic S)

- Cause less ocular irritation compared to Solution.
- Less effective when compared to Timolol
- Advantage it is selective beta blocker – **can be used in patients with pulmonary disease.**

Betaxolol properties

- May possess calcium channel blocker properties
- Thus may have neuroprotectic effect*
- Highly lipid soluble, binds well with plasma proteins
  - Significance: Lower CNS effects when compared to timolol

Osborne NN, Cazevieille C, Carvalho AL, et al. In vivo and in vitro experiments show that betaxolol is a retinal neuroprotective agent. Brain Res. 1997;751:113–123.

Wood JP, DeSantis L, Chao HM, Osborne NN. Topically applied betaxolol attenuates ischaemia-induced effects to the rat retina and stimulates BDNF mRNA. Exp Eye Res. 2001;72(1):79–86.

Metoki T, Ohguro H, Ohguro I, Mamiya K, Ito T, Nakazawa M. Study of effects of antiglaucoma eye drops on N-methyl-D-aspartate-induced retinal damage. Jpn J Ophthalmol. 2005;49(6):453–461.

Cheon EW, Park CH, Kim YS, et al. Protective effects of betaxolol in eyes with kainic acid-induced neuronal death. Brain Res. 2006;1069(1):75–85. Epub 2006 Jan 4.

Side effects

Local side effects

- Propranolol – corneal anesthesia
- Other OBBs no such effect.
- Discomfort, burning stinging
  - Factors like
    - Active molecule, pH, preservative and vehicle.
- Preservative- BAK
  - BAK helps with penetration of OBBs
  - Sensitivity not uncommon
  - Preservative free timolol is available (very expensive)

Local side effects- cont…

- Decreased tear production
- Decreased goblet cell density
- Dry eye symptoms
- Ocular cicatrical pemphigoid.

BAK issues multiplies beta blockers issues

Transient blurring with gel form (all gels not exclusively problem with OBBs)

Metipranolol associated with granulomatous uveitis (at least 4 publications)

Systemic side effects

- OBBs enter systemic circulation via nasolacrimal system
  - Almost like intravenous dose of medication
- Does not approach oral dose

- Typical dose 20-60 mg PO (oral dose)

First pass hepatic metabolism

50% approx 10 to 30 mg

Peak plasma values 50-103 ng/milli liter
Trough plasma values 0.8-7.2 ng/milli liter

Timolol 0.5% BID

Each drop is 30 micro liter (assume full absorption)
1 micro liter = 5 micro gram
30 micro liter = 150 micro gram
Two eye = 300 micro gram
Twice daily = 600 micro gram

Thus total systemic burden = 6% of a 20 mg oral dose
Two drops of timolol: plasma levels range 5.0-9.6 ng/milli liter

CNS adverse effects

- Detailed history is required
- Anxiety, depression, fatigue, lethargy, confusion, sleep disturbance, memory loss and dizziness
- Sexual dysfunction
- Decreased libido men and women
- Impotence in men

- CNS fewer with the use of betaxolol

Cardiovascular adverse effects

- Blocking beta-1 receptors interferes with normal sympathetic stimulation of heart
- Beta blockers
  - Lower heart rate
  - Lower blood pressure
  - Decreased myocardial contractility
  - Slowed conduction time

Topical OBBs – Cardiovascular effects

- Decreased heart rate and significant bradycardia
- Reduced blood pressure
  - **Always check BP and pulse rate on patients prescribed or on OBBs**
- Betaxolol –relative cardioselective- Not free from these effects

- Timoptic XE and other gels less effect-
  - **Gels stay in eye and decreased systemic absorption.**

Pulmonary adverse effects

- Most problems were early on due to lack of experience with OBBs
- 12 deaths in first 8 years; 50% of these had pulmonary disease
- Pulmonary effects due to- blockade to Beta-2 receptors.
- **Betaxolol has been used safely in patients with pulmonary disease.**

Metabolic adverse effects

- Affects lipid metabolism
- Normal volunteers used timolol:
  - 12% increase in triglycerides
  - 9% decrease in HDL
  - **Not all studies showed this effect**
- Data on OBBs and lipids inconclusive.

Drug disease interaction- CNS

- Depression -1960s and 1970s
- Subsequently large scale population based studies
  - No effect

No robust evidence for use of OBBs and depression- evaluate case by case

Drug disease interaction- cardiovascular and pulmonary disease

- Cardiovascular disease- contraindicated
  - May worsen BP- potentially worsening orthostatic hypotension, cerebrovascular disease, preripheral vascular disease.
- Pulmonary disease caution
- Anyone on OBBs develops these- alter medications
  - May relieve symptoms/ conditions

Drug disease interaction- Diabetes

- Symptoms of hypoglycemia
  - nervousness,
  - sweating,
  - intense hunger,
  - trembling,
  - weakness,
  - palpitations
- Beta blockers alter some of these – so masks effects
- **A true problem in insulin dependent patients**

Adrenergic agents- Alpha selective agonists

Adrenergic agents

- Clonidine
  - Lowers IOP well- but
    - Causes sedation
    - Systemic hypotension
    - Narrow therapeutic index
- Apraclonidine
- Brimonidine

Pharmacology Apraclonidine

- More hydrophillic
  - Does not penetrate eyes and blood brain barrier
  - More apha-2 selective
  - Wide therapeutic index
- Mechanism of action
  - Decreased aqueous production
  - Improves trabecular outflow
  - Decreases episcleral venous pressure

Uses of Apraclonidine

- FDA approved to prevent post laser treatment spikes in IOP
- Adjunctive therapy- TID

Brimonidine

- Highly apha-2 selective drug
- Mechanism of action
  - Reduction of aqueous production and uveoscleral outflow and reduction in episcleral venous pressure
- Peak effectiveness in 2 hours
- Effect present at lower amount at 8 hours
- Thus TID dose

Indications

- Prophylactic –to avoid post laser IOP spike
- Primary or secondary therapy glaucoma and ocular hypertension

Contraindications

- Allergy to drug
- Contraindicated in patients receiving monoamine oxidase (MAO) inhibitor therapy.

Adverse reaction

- Conjunctival follicles, ocular allergic reactions, and ocular pruritus (itching).
- headache, blurring, foreign body sensation, fatigue/drowsiness,
- Oral dryness,
- Ocular hyperemia, burning and stinging,

Combigan

- Brimonidine and timolol- BID (twice daily)

Other combination therapies

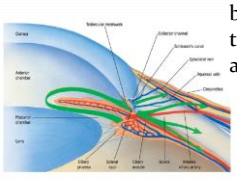
- Cosopt- dorzolamide and timolol- BID

Cholinergic drugs

Older drugs may have some use

- Pilocarpine
- Mainly angle closure glaucoma with pupillary block

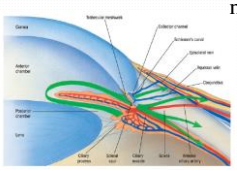
Mechanism of action



- Anatomic relationship between anterior tendons of ciliary muscle and
  - Scleral spur
  - Peripheral cornea
  - Trabecular meshwork
  - Inner wall of schlems canal

Mechanism of action

- Contraction of ciliary muscle causes
  - Unfolding of meshwork
  - Widening of Schlemm's canal



- Angle closure with pupillary block
  - 1 or 2% two to 3 times in 30 minutes

Systemic toxicity

- Extremely rare

- If occurs
  - Sweating
  - Salivation and
  - Gastrointestinal over activity

  - Atropine is pharmacological antagonist for pilocarpine

Containdications

- Risk/ history of retinal detachment
- Intraocular congestion like uveitis
- Any one whom pupil size and accommodation is an issue

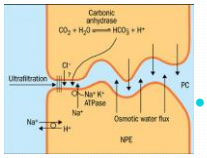
Combination

- Can be combined with drugs that decrease aqueous humor production

Carbonic anhydrase inhibitors (CAI)

Members of sulfonamide family

Mechanism of action



- Carbonic anhydranse inhibitors causes reduction of bicarbonate ions in posterior chamber
- Subsequently prevents Na+ movement and hence water movement

Oral Carbonic anhydrase inhibitors (CAI)

- Acetazolamide max dose 250mg qid
- Methazolamide max dose 150 mg bid

Contraindications

- Sulpha allergies
- Diabetic patients susceptible to ketoacidosis

- hepatic insufficiency and cannot tolerate the increase in serum ammonia
- Chronic obstructive pulmonary disease, in whom increased retention of carbon dioxide can cause potentially fatal narcosis from a combination of both renal and respiratory acidosis

Side effects

- Many well-known ocular and systemic side effects occur with administration of all the CAIs.
- These include **numbness**, paresthesias, malaise, **anorexia, nausea, flatulence, diarrhea, depression,** decreased libido, poor tolerance of carbonated beverages, myopia, hirsutism, increased serum urate, and, rarely, thrombocytopenia and idiosyncratic aplastic anemia

Table 6.2 Carbonic Anhydrase Inhibitors

Drug	Concentration	Route	Dosage
Acetazolamide[a]			
Diamox[a]	125-mg and 250-mg tablets	Oral	qid
Diamox Sequels	500-mg capsules	Oral	bid
Methazolamide[a]			
Neptazane[a]	25, 50, 100 mg	Oral	bid, tid
Dorzolamide HCl[a]			
Trusopt	2.0%	Topical	bid, tid
Brinzolamide[a]			
Azopt	1%	Topical	bid, tid

[a]Generic available.

TOPICAL AGENTS -CAI

- Dorzolamide
- Brinzolamide
- BID or TID
- Three times daily gives better reduction in intraocular pressure approximately one (1) -mmHg

Lowering IOP in office

Medical treatment- Goals

Angle closure

- Lower intraocular pressure
- Alleviate pain
- Clear cornea
- Prevent synechiae

No angle closure

- Lower IOP
  - Patient does not have pain
  - Patient does not usually have corneal edema
  - Angle open

Intravenous medications

- Acetazolamide 500mg intravenous
- Intravenous Mannitol

- Best therapy however is not always available in clinics

Treatment protocol-Acute angle closure

- Alpha -2 agonist- Brimonidine
- Beta blocker- Timolol (caution in asthmatics) or Betaxolol
- Carbonic anhydrase inhibitor – Dorzolamide (Caution sulpha allergy contraindication)
- Each medication given every 15 minutes

Oral medications

- Oral Carbonic anhydrase inhibitor
- Two tablets of 250 mg acetozolamide (Caution sulpha allergies contraindication)
- Works good when patient can retain medication - Vomiting common with angle closure glaucoma

- Check intraocular pressure after 1 hour if less than 40 mmHg
- Add Pilocarpine every 15 minutes for 45 minutes and repeat procedure ABC procedure
- Seek ophthalmologist opinion-refer patient

Take home medication

- Prednisolone acetate 1% q1-6 hours (approx every 3 hours)
- Acetazolamide 500 mg sequel BID
- Alpha agonist or beta blocker BID
- Pilocarpine 2% QID

Laser therapy

Procedure	Laser used	Indications
Iridotomy	Nd:YAG Argon Sequential argon-ND:YAG	Occludable angle Contralateral eye of an acute ACG Narrow or closed angle in more than 180 degrees with optic nerve damage and high IOP Acute ACG
Peripheral Iridoplasty	Argon	Plateau iris In preparation for laser trabeculoplasty After iridotomy if iris apposition is still present Before an iridotomy, in cases of thick, inflamed or rubeotic irises.

Generics versus brand name

Available online at www.sciencedirect.com
ScienceDirect
Research in Social and Administrative Pharmacy 8 (2012) 574–578
RESEARCH IN SOCIAL & ADMINISTRATIVE PHARMACY
ELSEVIER

Research Briefs

Generic medications for you, but brand-name medications for me

Amy J. Keenum, D.O., Pharm.D.[a,*], Jennifer E. DeVoe, M.D., D.Phil.[b], Deena J. Chisolm, Ph.D.[c], Lorraine S. Wallace, Ph.D.[d]

The title summarizes our feeling
Despite the obvious financial benefit

Generic

- Latanoprost
- Dorzolamide
- Numerous beta blockers
- Dozolamide/timolol combination (Cosopt)

Editorial

Ophthalmic Generics – Are They Really the Same?

Wiley A. Chambers, MD - *Silver Spring, Maryland*

In theory yes, in reality it depends

Issues with generics

- Drop size- may not be equivalent
- Variability of active ingredient
- Environmental exposure such as heat
- Reaction with plastic containers

ORIGINAL ARTICLE

A Comparison of Active Ingredients and Preservatives Between Brand Name and Generic Topical Glaucoma Medications Using Liquid Chromatography-Tandem Mass Spectrometry

Malik Y. Kahook[1], Robert D. Fechtner[2], L. Jay Katz[3], Robert J. Noecker[4], and David A. Ammar[1]

- Evaluated level of active ingredient
- Evaluated level of BAK
  - Baseline
  - At 30 days 25 degree Celsius (77 degree F)
  - At 30 days at 50 degree Celsius (122 degree F)

Current Eye Research, 37(2), 101–108, 2012

ISSN: 0271-3683 print/1460-2202 online
DOI: 10.3109/02713683.2011.631722

Effect of heat stress test

- Latanoprost
- Significant decrease compared to brand name in active ingredient
  - At 30 days both at 25 degree and at 50 degree C
- Dorzolamide/ timolol
  - Resistant to heat changes
- BAK concentrations at 50 degree C was decreased

Indian Journal of Ophthalmology

Year : 2007 | **Volume** : 55 | **Issue** : 2 | **Page** : 127--131

A randomized, crossover, open label pilot study to evaluate the efficacy and safety of Xalatan® in comparison with generic Latanoprost (Latoprost) in subjects with primary open angle glaucoma or ocular hypertension

Arun Narayanaswamy[1], Aditya Neog[1], M Baskaran[1], Ronnie George[1], Vijaya Lingam[1], Chetan Desai[2], Viraj Rajadhyaksha[2],

- In USA generics are new
- Outside USA not so much

Narayanaswamy et al., crossover trial

- Baseline drop
  - 38.6% with xalatan
  - 22.7% with generic latanoprost
- 8.86% loss of efficacy change from Xalatan to Latanoprost
- 4.3% increased efficacy change from generic to brand name

Generic versus brand-name North American topical glaucoma drops

Zaid N. Mammo, BSc*, John G. Flanagan, PhD, MCOptom†, David F. James, PhD‡, Graham E. Trope, FRCSC, MB, PhD§

They evaluated Timolol
when comparing brand name to generics
•drop volume
•viscosity
•surface tension
•bottle tip varied

Can J Ophthalmol 2012;47:55–61

Summary generic versus brand name

- Brand name offers more tighter control of the drug related issues
- Some drug is better than no drug and generics are here to stay

Preservatives and glaucoma medications

Medications and glaucoma

- Chronic drug uses and its effect on future surgical outcomes?
- Chronic combination therapies- significant risk factor for failure of trabeculectomy
  - Preservatives effect?
  - Inflammation leading to failure of future procedures*

- *Broadway DC et al., Adverse effects of topical antiglaucoma medications: II Arch Ophthalmol 1994

Summary

- Preservative free are better solution given the understanding we have.
- Non BAK preservatives may be a good trade off although not totally problem free.
- Prostaglandins don't need preservatives for drug penetration
- Some drug is better than no drug, preserved medications have a role to play in glaucoma management

Neuroprotection concepts

- Any method that prevents or slows the death of neurons is considered neuroprotective
  - In that definition all treatments are neuroprotective
- However when one talks about neuroprotection
  - Prevent destructive cellular events
  - Enhance survival of cells after damage

Drugs in neuroprotection

- None of the drugs that are approved for use in glaucoma patients
  - Indication of neuroprotection
  - Marketing claim of neuroprotection

So is there any evidence ?

Any drug –to be deemed neuroprotective

- Four criteria
  - 1) the agent must have a target in the retina;
    - Yes they are present
  - 2) it must be neuroprotective in animal models;
  - 3) it must reach neuroprotective concentrations in the posterior segment after clinical dosing;
  - 4) it must be shown to be neuroprotective in controlled clinical trials.