OCULAR HYPOTENSIVE AGENTS

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Overview

- Adrenergic agents
- Cholinergic agonists
- Carbonic anhydrase inhibitors
- Prostaglandin analogs
- Osmotic agents

- Mechanism of action
- Applications in human ophthalmology
- Applications in veterinary ophthalmology
Adrenergic agents

- β-blockers
- α₂-agonists
Sympathetic Innervation

- Terminal neurotransmitter = NE
- Receptors = $\alpha + \beta$
  - Iris dilator = $\alpha_1$
  - Iris sphincter = $\alpha_2 + \alpha_1 + \beta$
  - Trabecular meshwork = $\beta$
  - Ciliary body = $\alpha_1 + \alpha_2 + \beta$
AH Production

- Activation of $\beta$ receptors by NE $\rightarrow$ **increased** AH production

- Activation of $\alpha$ receptors by NE $\rightarrow$ **decreased** AH production
  - $\alpha$ receptors on effector cell are inhibitory for cAMP production
  - $\alpha$ receptors on neuron induce negative feedback, decreasing NE release

- Therefore, $\beta$-blockers and $\alpha$-agonists decrease AH production
β-Received

- G-protein linked
- Activate adenylate cyclase $\rightarrow$ produce cAMP $\rightarrow$ activate protein kinase A

- $\beta_1$-receptors = cardioactive

- $\beta_2$-receptors = AH production + smooth muscle relaxation (bronchi***)) + vasodilation

- $\beta_3$-receptors = lipolysis
**β-Blockers – Mechanisms**

1. Block CB β receptors → inhibit tonic influence of NE on cAMP production → decreased AH production

2. Inhibit active transport and ultrafiltration (Na+/K+-ATPase)

3. Vasoactive effect at iris root/CB
   - Do not alter AH drainage
   - Variable effect on retrobulbar/ocular blood flow
     - Possible increased positive effect in glaucoma?
**β-Blockers – ISA**

- **Intrinsic sympathomimetic activity**
  - Simultaneous inhibition and stimulation of β receptors
    - Ability to stimulate β-R while opposing stimulating effects of catecholamines
  - Depends on relative concentrations of β-blocker and NE at receptor
    - Stimulant effect when β-agonism is low (sleep)
    - Inhibitory effect when β-agonism is high (exercise)
  - Reduces risk of systemic effects (cardiovascular, respiratory) by allowing low-level agonism
  - Significance in topical ophthalmic preparations is unknown
  - Of topical ophthalmic formulations, carteolol has potential for greatest ISA
**β-Blockers – Neuroprotection**

- **Na⁺-channel blocking activity**
  - Ischemia → reduced ATP → failure of ATPase-driven pumps → \( \uparrow \text{Na}^+ \text{i} \) and \( \downarrow \text{K}^+ \text{i} \) → depolarization → reversal of \( \text{Na}^+ / \text{Ca}^{2+} \) exchange → \( \uparrow \text{Ca}^{2+} \text{i} \) → cellular demise + increase glutamate\(_e\)
  - \( \text{β} \)-blockers block \( \text{Na}^+ \) channels and subsequent intracellular \( \text{Na}^+ \) influx
  - Specific intracellular receptor on \( \text{Na}^+ \) channel that is bound determines degree of blockade
  - Betaxolol most effective

\( i = \text{intracellular} \)
\( e = \text{extracellular} \)

*Osborne NN, et al., JOPT 2005*
β-Blockers – Neuroprotection

- **Ca$^{2+}$-channel blocking activity**
  - Activation of receptor-operated and voltage-dependent L-type Ca$^{2+}$ channels + activation of ionotropic glutamate receptors $\rightarrow$ \( \uparrow \) Ca$^{2+}$, \( \rightarrow \) excitotoxicity

- β-blockers have Ca$^{2+}$ channel blocking ability
  - L-type Ca$^{2+}$ channels
  - Betaxolol most effective

\( i = \text{intracellular} \)

Osborne NN, et al., JOPT 2005
β-Blockers – Neuroprotection

- **Antioxidant activity**
  - Free-radical scavengers
  - Metoprolol is best

*Osborne NN, et al., JOPT 2005*
β-Blockers – Adverse ocular effects

- Local allergic reaction
- Membrane destabilization
  - Reduced corneal sensation
  - Superficial punctate keratitis
- Decreased TBUT
- Macular edema (aphakics)
- Uveitis
- Cataract progression

www.dryeyesummit.org
β-Blockers – Adverse systemic effects

- **Cardiovascular**
  - Bradycardia
  - Hypotension
  - Arrhythmias
  - Syncope

- **Pulmonary**
  - Bronchospasm
  - Dyspnea

- **CNS**
  - Amnesia
  - Depression
  - Headache

- **Dermatologic**
  - Rash
  - Urticaria
  - Nail discoloration
β-Blockers – Metabolism

- Systemic absorption up to 80% of drop
  - Known to produce adverse cardiovascular and respiratory effects

- Metabolized by CYP2D6 enzyme system
  - Predominantly hepatic
  - Minimal ocular

- Pharmacogenetic variations impact activity (thus metabolism) (PM, IM, EM, UM)

- Drug-drug interactions influence metabolism (fluoxetine, celecoxib, terbinafine, etc.)
β-Blockers – Contraindications

- Bronchial asthma
- Chronic obstructive pulmonary disease
- Bradycardia
- Severe heart block
- Overt cardiac failure
- Children and infants

Third degree heart block
**β-Blockers – Topical**

- **Non-selective (β₁ and β₂ receptors)**
  - Timolol (0.25%, 0.5%)
    - *Timoptic, Timoptic XE, Betimol, Istalol*
  - Levobunolol (0.25%, 0.5%)
    - *Betagan, Levobunolol HCl*
  - Metipranolol (0.3%)
    - *OptiPranolol*
  - Carteolol (1.0%)
    - *Ocupress*

- **Selective (β₁ receptors)**
  - Betaxolol (0.25%)
    - *Betoptic-S*
Timolol

- No ISA
- Mean IOP reduction in humans 25% - 40%
  - 0.25% and 0.5% formulations similar
  - Once daily in the am ≈ twice daily
  - Contralateral IOP also decreases
- More effective than pilocarpine or CAIs
- “Escape” = tolerance with long-term therapy

- **Formulations:**
  - Timolol XE = formulated in Gelrite
  - Istalol = formulated with potassium sorbate
  - Ocudose = unpreserved, single-dose vials
Timolol in Animals

- ~15 – 30% IOP reduction in dogs, cats, and horses

- Miosis, bradycardia, hypotension

- **Dogs:**
  - Greater reduction often requires increased concentration or combination
  - Dorzolamide, pilocarpine
  - Latanoprost…?

- **Cats:**
  - No greater reduction in combo with dorzolamide
  - Inconsistent reduction with gel-forming solution (once daily)

- **Horses:**
  - No greater reduction in combo with dorzolamide
**Timolol Contact Lenses in Dogs**

- **Comparison:**
  - Drop (x 5 days)
  - Contact + high or low drug - Vit E (x 24h)
  - Contact + high or low drug + Vit E (x 24h)

- All contacts → increased IOP-lowering effect versus drops
- No significant difference among contacts
- Less IOP reduction in contralateral eye with contacts
Levobunolol in Dogs

• **Alone:**
  - Less effective than when in combo with dorzolamide
  - Less effective than timolol + dorzolamide

• **Combo with dorzolamide:**
  - More effective than levo alone
  - More effective than timolol + dorzolamide

• Significantly reduces heart rate
Other β-Blockers

- **Carteolol**
  - Nonselective
  - Greater ISA

- **Betaxolol**
  - Selective for $\beta_1$ with significantly less sensitivity for $\beta_2$
  - Greater $\text{Na}^+$ channel blocking than other β-blockers
  - Greater L-type $\text{Ca}^{2+}$ channel blocking than other β-blockers
  - Vasodilation of ocular vessels
  - Inhibits glutamate-induced increase in intracellular $\text{Ca}^{2+}$
Sympathetic Innervation

• Terminal neurotransmitter = NE

• Receptors = $\alpha + \beta$
  • Iris dilator = $\alpha_1$
  • Iris sphincter = $\alpha_2 + \alpha_1 + \beta$
  • Trabecular meshwork = $\beta$
  • Ciliary body = $\alpha_1 + \alpha_2 + \beta$
\( \alpha_2 \)-Agonists

- Apraclonidine
  - 0.5%, 1%

- Brimonidine
  - 0.1%, 0.15%
  - 0.2% + 0.5% timolol

- Epinephrine
  - 0.25%, 0.5%, 1.0%, 2.0%

- Dipivalyl epinephrine
**α₂-Agonists**

- **Reduce AH production:**
  - Activation of presynaptic $\alpha_2$ receptors inhibits NE release
  - Activation of postsynaptic $\alpha_2$ receptors decreases intracellular cAMP

- **Increase uveoscleral AH outflow**

- **Also influence MMPs and TIMPs in trabecular meshwork, potentially lessening resistance to outflow**

- ($\alpha_1$ receptors also decrease CB blood flow and AH production)
α₂-Agonists – Neuroprotection

1. Direct interaction with α₂ receptors in RGC
   - Inhibition of apoptotic signaling cascade?
   - Direct reduction in extracellular glutamate

2. Block NMDA receptors from Ca\(^{2+}\)-induced excitotoxicity

3. Increase expression of neuroprotective brain-derived neurotrophic factor in RGC
   - Brimonidine is strongest in animal models

Kalapesi FB, et al., BJO 2005
Donello JE, et al., JPET 2001
Dong CJ, et al., IOVS 2008
Arthur S, et al., EER 2011
α₂-Agonists – Adverse ocular effects

- Irritation, hyperemia
- Mydriasis
- Follicular conjunctivitis
- Adrenochrome deposits
- Cystoid macular edema
$\alpha_2$-Agonists – Adverse systemic effects

- Hypertension
- Headache
- Cardiac arrhythmia
- Dry nose and mouth
- Fatigue
Apraclonidine

- Moderately selective for $\alpha_2$ receptors
- $\alpha_1$ activity affects ocular blood flow by inducing vasoconstriction
- Decreases AH production (initial), increases uveoscleral outflow (later), decreases episcleral venous pressure *

**Efficacy in humans**
- Reduces IOP by 30% to 40% at 3 – 5 hours for 12 hours
- Used perioperatively or for short-term reduction in patients on maximal therapy

**Side effects:**
- Development of tolerance – restricts clinical indications for use
- Ocular allergy common with chronic therapy (~50%)
- Dry mouth, dry nose (minimal effect on HR, BP, respiration)
- Activation of $\alpha_1$-receptors (eyelid retraction, mydriasis)

* Toris CB, et al., Ophthalmology 1995*
# Apraclonidine in animals

<table>
<thead>
<tr>
<th>Dosing regimen</th>
<th>Normal dogs *</th>
<th>Normal cats **</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.5% apraclonidine</td>
<td>0.5% apraclonidine</td>
</tr>
<tr>
<td></td>
<td>Single administration</td>
<td>Single administration</td>
</tr>
<tr>
<td>IOP decrease</td>
<td>16% (3 mmHg)</td>
<td>24% (4.8 mmHg)</td>
</tr>
<tr>
<td>Other</td>
<td>Mydriasis</td>
<td>Miosis</td>
</tr>
<tr>
<td></td>
<td>Conjunctival blanching</td>
<td>Bradycardia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bradycardia in 4/9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Vomiting in 8/9</td>
</tr>
</tbody>
</table>

* Miller PE, et al., AJVR 1996  
** Miller PE, et al., AJVR 1996
Brimonidline

- Highly selective for $\alpha_2$ receptors (30X more than $\alpha_1$ receptors)
- Decreases AH production (initial) and increases uveoscleral outflow (later)
- No effect on ocular blood flow
- Greatest neuroprotective effect
- Miosis following refractive surgery

**Efficacy in humans**
- 6.5 mmHg mean reduction
- Peak 2 hours post-dose, duration 12 hours
- Additive with other agents (3x daily dosing as monotherapy, 2x daily dosing in combo)

**Side effects**
- As for apraclonidine, except less mydriasis, less allergy
- Better tolerated systemically and ocularly
# Brimonidine in animals

<table>
<thead>
<tr>
<th></th>
<th>Glaucomatous Beagles *</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dosing regimen</strong></td>
<td>0.2% brimonidine one to three doses</td>
</tr>
<tr>
<td><strong>IOP decrease</strong></td>
<td>No consistent significant decrease</td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td>Miosis, Bradycardia</td>
</tr>
</tbody>
</table>

* Gelatt KN et al., Vet Ophthalmol 2002
Epinephrine and Dipivalyl Epinephrine

- **Epinephrine**
  - Mixed α- and β-agonist

- **Dipivalyl epinephrine**
  - Lipophilic prodrug of epinephrine
  - Converted by corneal esterases (acetylcholinesterase, cholinesterase, arylesterase)
  - Greater penetration with lower concentration (0.1%)

- **Mixed mechanisms**
  - *Increase AH production* *
    - β-receptor activity?
  - *No effect* on AH production **
  - *Decrease AH production***
    - Vasoconstriction
  - Increase trabecular outflow *, ***,
    - β-receptor activity?
  - Increase uveoscleral outflow ****

* Townsend DJ, et al., IOVS 1980
** Schneider TL, et al., IOVS 1991
*** Wang YL, et al., EER 1999
**** Schenker HI, et al., AO 1981
## Epinephrine and dipivalyl epinephrine in animals

<table>
<thead>
<tr>
<th></th>
<th>Normotensive cats *</th>
<th>Normotensive beagles **</th>
<th>Glaucmatous Beagles **</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dosing regimen</strong></td>
<td>2% epinephrine</td>
<td>1% or 2% epinephrine</td>
<td>0.5% dipivalyl epinephrine</td>
</tr>
<tr>
<td></td>
<td>q12h x 7 days</td>
<td>twice daily</td>
<td>twice daily</td>
</tr>
<tr>
<td><strong>IOP decrease</strong></td>
<td>7 mmHg (31%)</td>
<td>5 – 6 mmHg in glaucomatous Beagles</td>
<td></td>
</tr>
<tr>
<td><strong>Contralateral</strong></td>
<td>No decrease</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>untreated eye</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td>Reduction in AH</td>
<td>Irritation and tearing</td>
<td></td>
</tr>
<tr>
<td></td>
<td>production</td>
<td>with dipivalyl epinephrine</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Increase in AH</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>outflow</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Wang YL, et al., EER 1999
** Gwin RM, et al., AJVR 1978
Cholinergic agonists

- Parasympathomimetics
Parasympathetic innervation

- Neurotransmitter = acetylcholine
- Receptors = muscarinic
  - Ciliary body
  - Iris sphincter
- Synaptic enzyme = acetylcholinesterase
Parasympathetic influence on IOP

Stimulate muscarinic receptors
(iris sphincter + ciliary body) →
smooth muscle contraction
(miosis + accommodative spasm) → widening of scleral spur → opening of ICA →
increased AH drainage
Parasympathetic innervation

• Stimulation of muscarinic receptors → contraction of CB → decreased uveoscleral outflow + increased conventional outflow

• Conventional outflow increase > uveoscleral outflow decrease
Cholinergic agonists

**Direct-acting**
- Directly stimulate cholinergic receptors
  - Pilocarpine
  - Carbachol

**Indirect-acting**
- Inhibit acetylcholinesterase
  - Demecarium bromide
    - Carbamate
    - Reversible
  - Echothiophate
    - Organophosphate
    - Irreversible

*Fig. 1. After signalling, acetylcholine is released from receptors and broken down by acetylcholinesterase to be recycled in a continuous process.*
Cholinergic agonists side effects

- **Ocular**
  - Relatively common
  - Reduced visual acuity
    - Miosis, accommodative spasm
  - Permanent miosis
  - Cataract
  - Pupillary block glaucoma
  - Retinal detachment
Cholinergic agonists side effects

- **Systemic**
  - Perspiration/salivation
  - Headache/browache
  - Nausea
  - Vomiting
  - Bronchospasm
  - Pulmonary edema
  - Bradycardia
  - Systemic hypotension
Pilocarpine

- Stimulates M3 receptors
- pH 4.5 to 5.5
- 0.5%, 1%, 2%, 4%, 6% solutions
  - Four times daily dosing
  - Twice-daily with nasolacrimal occlusion
  - Higher concentrations necessary in eyes with darkly pigmented irides
- 4% gel (allows once-daily dosing)

**Indications:**
- Primary open-angle glaucoma
- Acute angle-closure glaucoma
- Secondary glaucomas
Pilocarpine in dogs

- IOP reduction generally 30 – 40%
- Greater reduction frequently requires increased concentration
- Greater reduction and increased consistency of reduction in combo with timolol
- Significant ocular irritation
- Miosis
- Tolerance develops with long-term use

- Doubles coefficient of outflow
  - 0.33 μL/min/mmHg to 0.61 μL/min/mmHg in normotensive dogs *
  - 0.15 μL/min/mmHg to 0.38 μL/min/mmHg in glaucomatous dogs *

Gum GG, et al., JSAP 1993
Krohne SG, AJVR 1994
Gwin RM, et al., IOVS 1977
Whitley RD, et al., AJVR 1980
Carrier M, et al., AJVR 1989
Gelatt KN, JOPT 1997
Gelatt KN, et al., AJVR 1995
Gelatt KN, et al., AJVR 1983
# Pilocarpine in cats and horses

<table>
<thead>
<tr>
<th></th>
<th>Normotensive cats *</th>
<th>Normotensive mares **</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dosing regimen</strong></td>
<td>2% Single dose</td>
<td>2% Single dose</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2% q12h x 5 days</td>
</tr>
<tr>
<td><strong>IOP decrease</strong></td>
<td>15% reduction</td>
<td>No reduction</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No reduction</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Trend toward increase</td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td>Miosis OU</td>
<td>Miosis</td>
</tr>
</tbody>
</table>

* Wilkie DA, et al., AJVR 1991
** Van der Woerdt A, et al., AJVR 1998
Carbachol

• Direct-acting
• Indirect-acting due to not being degraded by acetylcholinesterase → prolonged activity

• No epithelial penetration unless combined with surfactant
  • Ophthalmic solutions 0.75% to 3%
  • Often in combo with benzalkonium chloride
  • Intracameral injection versus topical administration

• Greater miosis and accommodative muscle spasm than pilocarpine
Intracameral carbachol in dogs

• Helpful…
  • 0.5 mL 0.01% following phacoemulsification +/- IOL implantation
  • No treated eyes developed POH, versus 12/16 controls 3h post-op

• Not so helpful…
  • 0.3 ml 0.01% carbachol versus latanoprost versus no tx following phacoemulsification
  • Significantly greater IOP 2 hours post-op following carbachol versus no tx

*Stuhr CM, et al., JAVMA 1998
Effect of intracameral administration of carbachol on the postoperative increase in intraocular pressure in dogs undergoing cataract extraction

Effect of three treatment protocols on acute ocular hypertension after phacoemulsification and aspiration of cataracts in dogs
Manuela Crasta,* Alison R. Glode†, Richard J. McMullen Jr.,† Diana O. Pate† and Brian C. Gilger†
Indirect-acting agents

- **Demecarium bromide**
  - Reversible (carbamate)
  - Increases facility of outflow by average 121% in glaucomatous eyes
  - Efficacy in humans:
    - IOP reduction 3 – 11 mmHg within 24 hours in normal eyes
    - IOP reduction ~50% in glaucomatous eyes

- Use limited by side effects
  - Significant brow-ache
  - Blurred vision
  - Nausea, vomiting, diarrhea
  - Salivation, sweating
  - Bradycardia
Demecarium bromide in dogs

• IOP reduction 30 – 40%

• Effective as prophylaxis in normotensive contralateral eye in dogs with closed-angle glaucoma

• Treatment with 0.25% demecarium bromide q12h in eyes with primary lens instability
  - Significantly delayed luxation in treated versus untreated eyes
  - No significant difference in time to luxation of contralateral eye, time to glaucoma, or time to vision loss

• Induces flare in normal eyes at initiation of treatment (lesser degree than pilocarpine)

Gum GG, et al., AJVR 1993
Miller PE, et al., JAAHA 2000
Dees EE et al., VO 2014
Binder DR, et al., JAVMA 2007
Krohne SG, AJVR 1994
Carbonic Anhydrase Inhibitors
Carbonic Anhydrase

$\text{CO}_2 + \text{H}_2\text{O} \rightleftharpoons \text{H}_2\text{CO}_3 \rightleftharpoons \text{H}^+ + \text{HCO}_3^-$

I = catalyzed by carbonic anhydrase

II = rapidly occurring ionic dissociation (no enzyme necessary)
Carbonic Anhydrase

- $\text{Na}^+ \text{ and } \text{Cl}^- \text{ actively transported}$
  - CB stroma $\rightarrow$ PE $\rightarrow$ NPE

- $\text{Na}^+ + \text{Cl}^- + \text{K}^+ + \text{HCO}_3^- \ (\text{formed following action of CA})$
  - NPE $\rightarrow$ PC $\rightarrow$ H$_2$O follows $\rightarrow$ AH

- Inhibition of formation of $\text{HCO}_3^-$ requires 100% inhibition of CA
# Carbonic Anhydrase

<table>
<thead>
<tr>
<th>Isoenzyme</th>
<th>Cellular location</th>
<th>Ocular location (humans)</th>
<th>Other location (humans)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CA I</td>
<td>Cytosolic</td>
<td>Lens Corneal endothelium</td>
<td>Red blood cells</td>
</tr>
<tr>
<td>CA II</td>
<td>Cytosolic</td>
<td>Lens Corneal endothelium Ciliary processes Retina</td>
<td></td>
</tr>
<tr>
<td>CA IV</td>
<td>Membrane-bound</td>
<td>Lens Choriocapillaris Retina</td>
<td>Kidney</td>
</tr>
</tbody>
</table>
Carbonic Anhydrase Inhibitors (CAI)

- **Systemic:**
  - Acetazolamide
  - Methazolamide

- **Topical:**
  - Dorzolamide
  - Brinzolamide

Fig. 1. Chemical structures of dorzolamide and brinzolamide.
CAI – General

- Activity versus CA II most important for reducing AH production
- Must inhibit essentially 100% of CA II in NPE to decrease formation of HCO$_3^-$ and subsequent formation of AH
- Increase retinal blood flow when applied topically
- Pigment binding serves as reservoir
- Minimal uptake by red blood cells minimizes systemic electrolyte and acid-base disturbances with long-term use in humans
CAI – General

IC$_{50}$ (nM) of selected CAI versus human CA isoenzymes *

<table>
<thead>
<tr>
<th></th>
<th>CA I</th>
<th>CA II</th>
<th>CA IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetazolamide</td>
<td>13.9</td>
<td>3.4</td>
<td>14.7</td>
</tr>
<tr>
<td>Methazolamide</td>
<td>4.7</td>
<td>8.1</td>
<td>80.3</td>
</tr>
<tr>
<td>Dorzolamide</td>
<td>600</td>
<td>0.18</td>
<td>6.9</td>
</tr>
</tbody>
</table>

IC$_{50}$ (nM) of selected CAI versus human CA isoenzymes **

<table>
<thead>
<tr>
<th></th>
<th>CA I</th>
<th>CA II</th>
<th>CA IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetazolamide</td>
<td>657</td>
<td>9.04</td>
<td>33.1</td>
</tr>
<tr>
<td>Dorzolamide</td>
<td>28,032</td>
<td>3.74</td>
<td>32</td>
</tr>
<tr>
<td>Brinzolamide</td>
<td>1,367</td>
<td>3.19</td>
<td>45.3</td>
</tr>
</tbody>
</table>

* Sugrue MF. PRER 2000
** DeSantis L. Surv Ophthalmol 2000
CAI – Systemic side effects

- **Metabolic acidosis**
  - Reduced retention of $\text{HCO}_3^-$ in kidneys
  - Reduced absorption of $\text{Na}^+$
  - Increased urinary excretion of $\text{K}^+$
  - Diuresis

- **Allergic reaction**
- **Cytopenias**
- **Gastrointestinal disturbances**
- **Fatigue**
CAI – Systemic side effects

- Electrolyte or acid-base disturbances are rare
  - Topical CAI preferential for CA II, therefore minimal uptake by red blood cells which have CA I

- Bitter taste (25%)
- Headache
- Nausea
- Fatigue
- Paresthesia
- Urolithiasis
- Skin rash
CAI – Ocular side effects

- **Allergic reaction**
  - Stinging/burning, itching, tearing, conjunctivitis, blepharitis (< 15%)
  - True allergy uncommon

- **Corneal toxicity (CA I and II)**
  - No increased corneal thickness or decreased endothelial cell counts with short- or long-term use in humans
  - Possible detrimental effects in severely devitalized corneas (pre-existing endothelial disease)

- **Lens toxicity (CA I, II, IV)**
  - Enzymes are ‘nonessential’ in lens
  - No deleterious effects in lens associated with ion movement
CAI – Contraindications

- Hypersensitivity to sulfonamides
- Renal disease
- Diabetic patients susceptible to DKA
- Hypokalemia
- Hepatic insufficiency
- Chronic obstructive pulmonary disease
  - Inability to compensate for metabolic acidosis by breathing off CO₂
- Pregnancy
## Oral CAI

<table>
<thead>
<tr>
<th>Acetazolamide</th>
<th>Methazolamide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Well-absorbed, highly protein bound</td>
<td>Improved partition coefficient</td>
</tr>
<tr>
<td>Three- to four-times daily dosing</td>
<td>Decreased protein binding</td>
</tr>
<tr>
<td>IOP reduction (30 – 50%) parallels plasma concentrations</td>
<td>Hepatic metabolism</td>
</tr>
<tr>
<td>Generally reserved for short-term IOP reduction in humans (i.e., acute angle-closure glaucoma)</td>
<td>→ increased absorption and distribution → smaller dose administered for clinical effect → lesser renal effects</td>
</tr>
<tr>
<td>Only 26% of patients can tolerate &gt; 6 weeks of therapy</td>
<td>Twice-daily dosing</td>
</tr>
<tr>
<td>IOP reduction (30 – 50%) parallels plasma concentrations</td>
<td></td>
</tr>
</tbody>
</table>
Acetazolamide and Methazolamide in Animals

- Significant IOP reduction (20 – 30%) in glaucomatous dogs and cats
- No greater increase in eyes also receiving topical dorzolamide
- Metabolic acidosis, particularly in cats
- Rapidly absorbed following PO administration in horses
- Relatively low bioavailability in horses
- Unknown effects on IOP in horses

Gelatt KN, et al., AJVR 1979
Alberts MK, et al., AJVR 2000
Gelatt KN, et al., AJVR 1979
Skorobohach B, et al., AJVR 2003
Dorzolamide

- Lipophilic and hydrophilic
  - Penetrates to posterior segment
  - Acidic pH (~5.8)

- Monotherapy
  - Indicated for q 8 h dosing
  - Consistent IOP reduction in humans with 2% solution (~20% reduction)

- Combination therapy
  - Additive with other topical ocular hypotensives
  - Can be administered q 12 h in combo
Dorzolamide in Animals

- **Dogs:**
  - IOP reduction 25 – 35%
  - Increased in combo with timolol

- **Cats:**
  - Inconsistent IOP reduction in normal cats
  - 38% IOP reduction in glaucomatous cats
  - Dampens circadian IOP fluctuation
  - Decreases AH flow rate in normal cats

- **Horses:**
  - 2 mmHg reduction in normal horses

References:

- Cawrse M, et al., AJVR 2001
- Willis AM, et al., AJVR 2001
- Rankin AJ, et al., AJVR 2012
Brinzolamide

- Greater lipophilicity than dorzolamide
- Less acidic

- Topical administration $\rightarrow$ intraocular levels greater than necessary for therapeutic efficacy

- Wide safety profile for systemic toxicities
  - Substantial binding to CA I in red blood cells
  - Does not saturate RBC
  - Does not result in metabolic acidosis

- Increases ONH blood flow when applied topically to rabbits

* De Santis L. Surv Ophthalmol 2000
## Brinzolamide in Animals

<table>
<thead>
<tr>
<th></th>
<th>Normal dogs *</th>
<th>Normal cats **</th>
<th>Normal horses ***</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dosing regimen</strong></td>
<td>1%</td>
<td>q12h x 7 days</td>
<td>Once to twice daily x 3 days</td>
</tr>
<tr>
<td><strong>IOP decrease</strong></td>
<td>Mean 3.5 mmHg</td>
<td>None</td>
<td>14% - 21%</td>
</tr>
</tbody>
</table>

* Whelan NC, et al., Proc ACVO, 1999  
*** Germann S, et al., EVJ 2008
Prostaglandin Analogs

Diacylglycerol or phospholipid

Phospholipase C  Phospholipase A₂

Arachidonic acid

Lipoxygenase (FLAP, Alox5)

HPETE (hydroperoxyeicosatetraenoic acid)

PGH₂ synthase (cox-1 or -2, COX-1 or -2)

H₂O

Leukotriene A₄

Leukotriene C₄

Glutathione

Glutathione S-transferase

Leukotriene D₄

Leukotriene E₄

Prostaglandin H₂ (PGH₂)

PGD₂

PGE₂

PGF₂

Prostacyclin (PGI₂)

Thromboxane (TXA₂)

Prostaglandin synthase

PGE synthase

Prostacyclin synthase

Thromboxane synthase
Prostaglandins

- **Prostaglandins** = PGD$_2$, PGE$_2$, PGF$_{2\alpha}$, PGI$_2$
- **Receptors** = DP, EP, FP, IP
- **PGF$_{2\alpha}$** (FP receptors) most effective ocular hypotensive
- **EP receptors** also mediate ocular hypotension

---

**Table 1**

<table>
<thead>
<tr>
<th>Receptor Subtype</th>
<th>Second Messenger</th>
<th>Ocular Tissue Distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>DP$^9$</td>
<td>↑cAMP</td>
<td>retina$^9$</td>
</tr>
<tr>
<td>EP$_1^{22}$</td>
<td>↑[Ca$^{2+}$]i</td>
<td>ciliary body, iris sphincter$^{38}$</td>
</tr>
<tr>
<td>EP$_2^{47}$</td>
<td>↑cAMP</td>
<td>?</td>
</tr>
<tr>
<td>EP$_3^{6,46,49}$</td>
<td>↓cAMP, ↑[Ca$^{2+}$]i</td>
<td>trabecular meshwork, ciliary muscle$^{23}$</td>
</tr>
<tr>
<td>EP$_4^{5,7}$</td>
<td>↑cAMP</td>
<td>NPE and ciliary muscle cells$^{38}$</td>
</tr>
<tr>
<td>FP$^2$</td>
<td>↑[Ca$^{2+}$]i</td>
<td>ciliary muscle$^{38,43}$</td>
</tr>
<tr>
<td>IP$^{38}$</td>
<td>↑cAMP</td>
<td>?</td>
</tr>
<tr>
<td>TP$^{28,45}$</td>
<td>↑[Ca$^{2+}$]i</td>
<td>corneal epithelium, ciliary processes, retina$^{14}$</td>
</tr>
</tbody>
</table>

Prostaglandin Analogs

- Ester prodrugs of PGF$_{2\alpha}$
  - Latanoprost
  - Travoprost
  - Unoprostone

- Converted by corneal esterases →
  - 17-phenyl-PGF$_{2\alpha}$
  - Free acid of isopropyl unoprostone

- Extreme specificity for FP receptors minimizes side effects associated with stimulation of other PG receptors
Prostamides

- Structurally related to prostaglandins, but neutral charge
- Synthesized from anandamide
  - Amide prodrug of 17-phenyl-PGF$_{2\alpha}$ = bimatoprost
- Little activity versus PG receptors
- No identified prostamide receptors exist
Prostaglandin Analogs

1. **Increase uveoscleral outflow**
   - Mediated by increased expression of MMPs and TIMPs
     - Relaxation of ciliary muscle (early)
     - Remodeling ECM of ciliary muscle and sclera to increase tissue spaces (late)

2. **Increase trabecular outflow facility**
   - Variable evidence
   - Mediated by endothelin-1
     - Relaxation of TM (early?)
   - Mediated by increased expression of MMPs and TIMPs, insulin-like growth factor-1, and fibroleukin
     - Remodel ECM of TM (late?)

*Toris CB, et al., Surv Ophthalmol 2008; Curran MP, Drugs Aging 2009*
PG Analogs – Side Effects

• Conjunctival hyperemia – vasodilation versus inflammation

• Eyelash darkening, thickening, and elongation
  • ~50% incidence with treatment duration 6 – 12 months
  • Relatively unpronounced, but can be extreme

• Iris darkening
  • Influence of coloration:
    • Yellow-brown (70%)
    • Green-brown (69%)
    • Blue/gray-brown (45%)
    • Brown (17%)
    • Blue/gray (8%)
  • Generally within 8 months of therapy
  • More likely in aged patients (> 75 years)

** Stjernschantz J, et al., Surv Ophthalmol 2002
PG Analogs – Contraindications

- Hypersensitivity
- Women who are pregnant or nursing
- Post-operative ocular inflammation?
- Cystoid macular edema?
- Herpes simplex keratitis
Latanoprost

- Labeled for once daily dosing
  - Most consistent IOP reduction (versus BID dosing)

- Peak IOP-lowering effect 8 – 12 hours post-administration

- More effective than timolol, $\alpha_2$-agonists, and CAI as monotherapy

- Contradictory evidence regarding effect on ocular blood flow

- Variable evidence regarding potential neuroprotective effects

*CM Perry, et al., Drug Aging 2003*
Latanoprost in Animals

• **Dogs:**
  - 30 – 60% IOP reduction
  - No difference in combo
    - Pilocarpine, timolol
  - Efficacy decreased in combo with flurbiprofen
  - Miosis, conjunctival hyperemia, flare
  - No effect in contralateral eye

• **Cats:**
  - Consistent miosis
  - 60% IOP reduction in PCG without reduction in AH flow

• **Horses:**
  - 0% - 17% IOP reduction
  - Miosis, conjunctival hyperemia, flare

Studer ME, et al., AJVR 2000
Carvalho AB, et al., VO 2006
Tofflemire KL et al., AJVR 2015
Gelatt KN, et al., VO 2001
Pirie CG, et al., Vet Ophthalmol 2011
ME Studer, et al., AJVR 2000
McDonald JE et al., VO 2015
Willis AM, et al., AJVR 2001
Davidson H, et al., Vet Ther 2002
Latanoprost in Dogs

- Single unilateral application followed by fluorophotometry

- **Latanoprost:**
  - 49% increase in AC fluorescein
  - 10% increase in untreated control
  - Significant

- **Dorzolamide/timolol:**
  - 38% increase in AC fluorescein
  - 24% increase in untreated control
  - Not significant
Latanoprost in Dogs

- IOP = AH inflow – uveoscleral outflow + EVP
  - Trabecular outflow

- Unilateral administration q24h x 21 days, episcleral venomanometer

- Increase in EVP with latanoprost in the dog
  - Latanoprost affects AH production and/or uveoscleral outflow
  - Latanoprost does not affect trabecular outflow
  - Episcleral AV shunting?
    - Side effect of conjunctival hyperemia?
    - Compensatory?
Travoprost

- Increases uveoscleral outflow, without effect on trabecular outflow or AH production

- Short-term treatment reduces IOP by ~ 30% versus baseline
- Long-term treatment
  - More effective than twice-daily timolol
  - Comparable or greater efficacy than once-daily latanoprost
  - Effective in combination with timolol

- More likely to produce conjunctival hyperemia than latanoprost (~40% versus ~30%)

- Should be dispensed in polypropylene containers

** Whitson JT. Expert Opin Pharmacother 2002
## Travoprost in Animals

<table>
<thead>
<tr>
<th>Dosing regimen</th>
<th>Normal dogs *</th>
<th>Glaucomatous dogs **</th>
<th>Glaucomatous dogs ***</th>
</tr>
</thead>
<tbody>
<tr>
<td>Travoprost q24h</td>
<td>Latanoprost q24h</td>
<td>q24h am or pm</td>
<td>0.00033% - 0.0033% travoprost</td>
</tr>
<tr>
<td></td>
<td></td>
<td>q12h 0.0001% travoprost</td>
<td>0.0001% travoprost</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>IOP reduction</th>
<th>Normal dogs *</th>
<th>Glaucomatous dogs **</th>
<th>Glaucomatous dogs ***</th>
</tr>
</thead>
<tbody>
<tr>
<td>45%</td>
<td>40%</td>
<td>60%</td>
<td>75%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>~50%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>17%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Other</th>
<th>Normal dogs *</th>
<th>Glaucomatous dogs **</th>
<th>Glaucomatous dogs ***</th>
</tr>
</thead>
<tbody>
<tr>
<td>Miosis</td>
<td>Miosis</td>
<td>Miosis</td>
<td>Miosis</td>
</tr>
<tr>
<td>Conjunctival hyperemia</td>
<td>Conjunctival hyperemia</td>
<td>Flare</td>
<td></td>
</tr>
</tbody>
</table>

* Carvalho AB, et al., Vet Ophthalmol 2006
* Gelatt KN, et al., Vet Ophthalmol 2004
Bimatoprost

- Labeled for once daily (evening) dosing
  - Greater efficacy than twice-daily timolol *
  - Comparable or greater efficacy than latanoprost or travoprost in people *
  - IOP reduction within 4 hours, maximum at 8 – 12 hours, duration 24 hours
  - Good evidence for increase in trabecular (as well as uveoscleral) outflow **,***

- Side effects:
  - Conjunctival hyperemia (slightly greater than with other PG analogs)
  - Ocular pruritus
  - Visual disturbance
  - Burning, foreign body sensation
  - Cataract
  - Eyelash and iris and eyelid darkening

* Curran MP, Drugs Aging 2009
** Christiansen GA, et al., Ophthalmol 2004
**Bimatoprost**

- Labeled for once daily (evening) dosing
  - Greater efficacy than twice-daily timolol *
  - Comparable or greater efficacy than latanoprost or travoprost in people
  - IOP reduction within 4 hours, maximum at 8 – 12 hours, duration 24 hours

**Side effects:**
- Conjunctival hyperemia (slightly greater than with other PG analogs)
- Ocular pruritus
- Visual disturbance
- Burning, foreign body sensation
- Cataract
- Eyelash and iris and eyelid darkening

* Curran MP, Drugs Aging 2009
Bimatoprost in Animals

<table>
<thead>
<tr>
<th></th>
<th>Glaucmatous Beagles *</th>
<th>Normal cats **</th>
<th>Normal cats **</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dosing regimen</strong></td>
<td>q24h am</td>
<td>q24h pm</td>
<td>q12h</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>q24h</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>q12h</td>
</tr>
<tr>
<td><strong>IOP decrease</strong></td>
<td>64%</td>
<td>66%</td>
<td>78%</td>
</tr>
<tr>
<td></td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td>q12h most consistent</td>
<td>No miosis</td>
<td>Miosis, followed by increase pupil diameter prior to next treatment</td>
</tr>
<tr>
<td></td>
<td>Miosis</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Unoprostone Isopropyl

- 0.012%
- 100-fold less potent at FP receptor than latanoprost *
- Comparable efficacy to q12h timolol
- Additive with other ocular hypotensive classes

## Unoprostone Isopropyl in Animals

<table>
<thead>
<tr>
<th></th>
<th>Normal dogs *</th>
<th>Glaucomatous Beagles **</th>
<th>Normal cats ***</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dosing regimen</strong></td>
<td>Single dose</td>
<td>q24h am</td>
<td>q24h</td>
</tr>
<tr>
<td></td>
<td></td>
<td>q24h pm</td>
<td>q12h</td>
</tr>
<tr>
<td></td>
<td></td>
<td>q12h</td>
<td>q24h</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>q12h</td>
</tr>
<tr>
<td><strong>IOP decrease</strong></td>
<td>5 mmHg (24%)</td>
<td>28% to 36%</td>
<td>No change</td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td>Miosis</td>
<td>Miosis</td>
<td>No miosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Significantly greater and more consistent with q12h dosing</td>
<td></td>
</tr>
</tbody>
</table>

* Ofri R, et al., JVIM 2000  
** Gelatt KN et al., JOPT 2004  
*** Bartoe JT, et al., Vet Ophthalmol 2005
Osmotic Agents

OSMOSIS

Diffusion of molecules from a place of higher concentration to a place of lower concentration until the concentration on both sides is equal.
Osmotic Agents

- Plasma tonicity > AH and VH tonicity →
  - Decreases ultrafiltration
  - Dehydrates vitreous
  - Posterior shift of lens-iris diaphragm → opens ICA

- Degree of IOP lowering determined by:
  - Ocular penetration
  - Distribution in body fluids
  - Molecular weight and concentration
  - Dosage
  - Rate and route of administration
  - Rate of systemic clearance
  - Type of diuresis
Osmotic Agents

**Indications:**
- Acute glaucoma
  - Angle-closure
  - Aqueous misdirection
  - Some secondary glaucomas
- Pre-operative preparation (intraocular surgery)
Osmotic Agents

- **Contraindications:**
  - Anuria
  - Severe dehydration
  - Pulmonary edema
  - Cardiac decompensation
  - Hypersensitivity
Osmotic Agents – Side Effects

- Rebound increase in IOP
  - Occurs when blood osmolality decreases with drug clearance
- Nausea
- Vomiting
- Headache
- CNS signs
  - Thirst, chills, lethargy
- Congestive heart failure
- Pulmonary edema
- Urine retention
- Electrolyte abnormalities
Osmotic Agents

- **Glycerol**
  - 50% or 75% solution for PO administration
  - 1 – 2 g/kg
  - Metabolized to glucose
  - Less diuresis than mannitol due to rapid metabolism

- **Mannitol**
  - 20% solution for IV administration
  - Concentrates within extracellular compartments
  - Minimally metabolized, excreted by kidneys
  - Use in normal dogs:
    - 1-2 g/kg IV over 20-30 min, withholding water
    - IOP reduction within 15 min, maximum of 9 mmHg 1.5 hours
Mannitol

- **Normal dogs:**
  - Significant decrease (3 mmHg) through 1 hour with mannitol
  - Significant decrease (2 mmHg) through 30 min with hetastarch
  - Significant increase at 120 and 180 min with hetastarch

- **Clinical cases:**
  - 7 mmHg to 21 mmHg (19% to 31%) reduction at 15 min with hetastarch
  - Increase up to 35% with hetastarch
Summary

- Understand autonomic innervation of the eye
  - Relate to mechanism of action of adrenergic and cholinergic agents
- Understand mechanisms of AH formation
  - Relate to mechanism of action of carbonic anhydrase inhibitors
- Understand mechanisms of AH drainage
  - Relate to mechanism of action of prostaglandin analogues

- Significant overlap in proposed IOP-lowering mechanisms
- Neuroprotection is an important factor to consider in glaucoma pharmacotherapy