**PHARMACOLOGY OF OPHTHALMIC AGENTS**

Introduction and Review

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**PHARMACOKINETICS**

*The study of the absorption, distribution, metabolism, and excretion of a drug or agent*

A drug can be delivered to ocular tissue:

- **Locally:**
  - Eye drop
  - Ointment
  - Periocular injection
  - Intracameral injection
- **Systemically:**
  - Oral
  - IM
  - IV

**Factors Affecting Drug Penetration into Ocular Tissues**

- **Drug concentration and solubility:** The higher the concentration the better the penetration, but limited by reflex tearing.
- **Viscosity:** Addition of methylcellulose and polyvinyl alcohol increases drug penetration by increasing the contact time with the cornea and altering corneal epithelium.
- **Lipid solubility:** Because of the lipid rich environment of the epithelial cell membranes, the higher lipid solubility, the more the penetration.

**SURFACTANTS:** The preservatives in ocular preparations alter cell membrane in the cornea and increase drug permeability, e.g., benzalkonium and thiomersal.

**pH:** The normal tear pH is 7.4; if the drug pH is much different, it will cause reflex tearing.

**Drug Tonicity:** When an alkaloid drug is put in relatively alkaloid medium, the proportion of the uncharged form will increase, thus more penetration.

**FLUORESCEIN**

Chemistry

- C_{20}H_{12}O_{5}, brown crystal
- M.W. 322.3
- Peak absorption 485-500 nm.
- Peak emission 520-530 nm.

**Dosage**

- **Adults:** 500-750 mg IV, e.g., 3 cc 25% solution, 5 cc 10% solution
- **Children:** 1.5-2.5 mg/kg IV
**Ophthalmic Pharmacology**

**Needle Diameter**

<table>
<thead>
<tr>
<th>Gauge</th>
<th>Outer Diameter (mm)</th>
<th>Inner Diameter (mm)</th>
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<tbody>
<tr>
<td>18</td>
<td>1.270</td>
<td>0.838</td>
</tr>
<tr>
<td>20</td>
<td>0.908</td>
<td>0.603</td>
</tr>
<tr>
<td>21</td>
<td>0.819</td>
<td>0.514</td>
</tr>
<tr>
<td>23</td>
<td>0.641</td>
<td>0.337</td>
</tr>
<tr>
<td>25</td>
<td>0.514</td>
<td>0.260</td>
</tr>
</tbody>
</table>

**Ideal Flow through a small tube varies with the 4th power of the radius (r^4)**

<table>
<thead>
<tr>
<th>Gauge</th>
<th>r</th>
<th>r^4</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>0.3015</td>
<td>0.090826</td>
</tr>
<tr>
<td>21</td>
<td>0.257</td>
<td>0.00436</td>
</tr>
</tbody>
</table>

\[
\frac{0.090826}{0.00436} = 1.895
\]

**FLUORESCEIN**

**Side Effects**

- Skin staining: 100% (6-12 hours)
- Aqueous staining: 100% (8-24 hours)
- Urine staining: 100% (24-36 hours)

**FLUORESCEIN ANGIOGRAPHY**

**Adverse Reactions**

Reported with:
- Topical phenylephrine
- Venipuncture
- Fundus photography

Do not change with:
- Informed consent
- NPO state
- Premedication
- Dye concentration

**FLUORESCEIN**

**Extravasation**

- Think prevention
- Warm, wet compress, 30 minutes Q.I.D.
- Examine site at 24°, 48°
- If avascular, refer to plastic surgeon

- Intense local pain
- Dull ache, ipsilateral extremity
  - Duration: 20 - 45 minutes
  - Management: self-limited reassurance
cold pack
- Dermal necrosis

**FLUORESCEIN**

**Intravenous**

Chemical thrombophlebitis
- Duration: 3-10 days
- Management: self-limited

Richard Alan Lewis, M.D., M.S. Nov 2013
**FLUORESCEIN Intra-arterial**
- Immediate INTENSE stain of distal extremity
- PAIN!
  - Duration: 1-24 hours
  - Management: Cold, Analgesia

**FLUORESCEIN ANGIOGRAPHY**

- **Mild Adverse Reactions**
  - Nausea and vomiting < 5%
  - Extravasation
  - Sneezing
  - Pruritus

- **Moderate Adverse Reactions**
  - Transient
  - Medical therapy required
  - Complete, if gradual, resolution with no sequelae

- **Severe Adverse Reactions**
  - Respiratory (1:3,800)
    - Laryngeal stridor, edema
    - Bronchospasm
    - Anaphylaxis
  - Cardiovascular (1:5,300)
    - Circulatory shock
    - Myocardial infarction, arrest
  - Neurological (1:13,900)
    - Seizure

  Overall: 1:1,900

- **Toxicity**
  - Phototoxicity to skin (Premature, jaundiced infant, UV therapy: J Peds: 1985; 107)

- **Death**
  - Death rate: 1:220,000
FLUORESCEIN Precautions
- Not approved for use in pregnancy
- No evidence for teratogenicity, embryocidicity
- Not approved for use in children
- Renal insufficiency prolongs elimination
- Diabetics should not confuse color with reactions for glucose

FLUORESCEIN Precautions
- Does NOT cross-react with iodinated contrast dyes
- Avoid patients with prior serious reactions to fluorescein
- Avoid historically risky patients

FLUORESCEIN Prophylaxis: Nausea
Metoclopramide HCl (Reglan) 20 mg IV 5 min before F/A

ADVERSE REACTIONS Management
- Trained personnel
- Emergency equipment
  - Airway (oral, AMBU)
  - O₂ (mask, prongs cylinder)
  - Parenteral fluids (I.V. stand, fluids, sets)
  - B/P cuff
  - Drugs

FLUORESCEIN ANGIOGRAPHY
Not routinely conducted on pregnant subjects

MANAGEMENT Screening
- Consent form, especially children
- History of prior allergies, asthma
  - A negative history is no guarantee of impunity
- History of recent change in angina, uncontrolled hypertension, cardiac arrhythmia

FLUORESCEIN ANGIOGRAPHY
Informed Consent

DRUGS for ANAPHYLACTOID REACTIONS
- Diphenhydramine (Benadryl) 25-50 mg p.o., i.m., i.v.
- Tripelennamine (Pyribenzamine) 25-50 mg p.o.
- Fexofenadine (Allegra) 180 mg. p.o.

Most serious reactions occur within minutes of injection. Severe anaphylactoid reactions may develop as late as one hour after injection.
Therefore, if there is any suspicion, the patient should wait and be observed.

INDOCYANINE GREEN

**Description**
Tricarbocyanine dye with peak spectral absorption at 800-810 nm, emission at 830-840 nm, in blood.

**Formulation**
- Contains 5% Nal
- pH 5.5 - 6.5
- Unstable in aqueous solution

**Chemistry**
\[ \text{C}_{43}\text{H}_{47}\text{N}_2\text{NaO}_6\text{S}_2 \]
\[ \text{M.W.} \ 774.96 \]

**Indications**
- Ophthalmic angiography
- Cardiac output
- Hepatic function, blood flow

**Dosage**
- 0.5 mg/kg (<2 mg/kg)
- Adults: 40 mg in 2 ml solvent with 5 cc N.S. flush

**Pharmacology**
- Bound to plasma proteins (albumin, 95%)
- Hepatic secretion to bile

**Contraindications**
- Diluent contains Nal
- Avoid allergy to iodides

**Adverse Reactions**
- Anaphylaxis, urticaria reported, without allergy to iodides
- 2 deaths reported
**Iodine/Iodide Allergy**

*NO objective evidence demonstrates cross-reactivity between allergy to shellfish and iodine sensitivity!*


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**INOCYANINE GREEN**

**Pregnancy**

*Safety in pregnancy, nursing not established*

*No animal embryocidity, teratogenicity studies*

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**VERTEPORFIN**

**Trade Name:** Visudyne

**formula:** $C_{41}H_{42}N_4O_8$

*Isomers of benzoporphorin*

*Molecular Weight: 718.8*

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**VERTEPORFIN**

**Indication**

*Light-activated drug for photodynamic therapy of various subretinal neovascularizations*

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**VERTEPORFIN**

**Metabolism**

*Liver excretion into bile, feces*

*Half-life 5-6 hours*

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**VERTEPORFIN**

**Adverse Reactions**

- Skeletal: back pain, 2-15%
- Skin: photosensitivity (5 days)
- GI: nausea
- CV: syncope, hypotension, bradycardia

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**VERTEPORFIN**

**Contraindications**

*Porphyria*

*Liver dysfunction*

*Known hypersensitivity*

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**VERTEPORFIN**

**Other Cautions**

*Pregnancy class C*

*Rats: anophthalmia*

*Avoid nursing*

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**VERTEPORFIN**

**Precautions**

*Photosensitization, ~ 5 days*

*Avoid extravasation*

*Matched laser 689 nm.*
VERTEPORFIN
Cautions
- Avoid other photosensitizers (thiazides, sulfas, antidiabetics)
- 83 sec. treatment, exactly 15 min. after 10 min. infusion

PEGAPTANIB
- Trade name: Macugen
- Formula: $C_{294}H_{342}F_{13}N_{107}Na_{28}O_{188}P_{28}$
  
  $[C_2H_4O]_n$, where $n \approx 900$
- Molecular Wt: ~50 kD

PEGAPTANIB
- Mechanism of Action: Selective antagonist of Vascular Endothelial Growth Factor (VEGF)

PEGAPTANIB
- Mechanism: An aptamer, modified RNA oligonucleotide, that adopts the 3-dimensional conformation to bind to extracellular VEGF$_{165}$, inhibiting its binding to VEGF receptors.

PEGAPTANIB
- Dose: 0.3 mg intravitreous
- Frequency: Every 6 weeks
- Half-life: ~10 days
- Metabolism: Degraded by nucleases

PEGAPTANIB
- Indication: ‘Wet’ macular degeneration
- Contraindications: ocular infections; known sensitivity

PEGAPTANIB
- Pregnancy: Not studied
- Nursing: Not studied
- Children: Not studied
- Safety or efficacy not proven beyond 2 years

RANIBIZUMAB
- Trade name: Lucentis
- Formula: recombinant humanized IgG1 κ monoclonal antibody fragment
- Molecular wt.: 48 kD
**RANIBIZUMAB (Lucentis)**

- **Indication:** “Wet” macular degeneration
- **Contraindications:** sensitivity; active ocular infections
- **Dose:** 0.5 mg intravitreous
- **Frequency:** q month x 4, then q 3 months
- **Half-life:** 7 – 12 days
- **Mechanism of action:** Binds to all receptor binding sites of VEGF-A, preventing interaction of VEGF with its receptors.
- **Cautions:** Transient elevation of intraocular pressure; endophthalmitis; thromboembolic events (<4%)
- **Side Effects:** subconjunctival hemorrhage, pain, v. floaters, elevated IOP, intraocular inflammation

**BEVACIZUMAB (Avastin)**

- **Trade name:** Avastin
- **Formula:** complete humanized IgG monoclonal antibody
- **Molecular wt.:** 149 kD
- **Dose:** 1.25 – 2.5 mg. intravitreous
- **Frequency:** every 4 weeks
- **Half-life:** 20 days (11-50 d)
- **Metabolism:** ? Nucleases
- **Excretion:** ?
**BEVACIZUMAB**

**Avastin**

- **Indications:** OFF LABEL: “Wet” macular degeneration; CNV, NVG, PDR, ROP, C/BRVO, diabetic macular edema

**Mechanism of Action:**
- Binds competitively to VEGF receptors blocking VEGF’s activity

**Side Effects:** risk of bleeding

**Cost:** among the most expensive drugs in the world, widely marketed!

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**EYLEA:**

**Mechanism**
- Soluble “decoy-receptor” of both VEGF-A and Placental Growth Factor (PlGF)

**Schedule**
- Intravitreous injection
- Q 4 weeks x 3; then
- Q 8 weeks for ~1 year

**Aflibercept (EYLEA)**

**Potential Risks**
- Failure to control CNV
- Endophthalmitis
- Retinal Detachment
- Transient elevation of IOP
- ?Thromboembolism?

**Pregnancy Class C**
- Nursing mothers?
- Pediatric population?
- Mutagenesis?
- Carcinogenesis?

**Routes of Administration:**

**Topical**
- Most ocular medications are delivered topically - maximizes anterior segment concentrations and minimizes systemic toxicity;
- Drug gradient from tear reservoir to corneal and conjunctival epithelium forces passive absorption.

**Factors affecting absorption:**
- Drug concentration (limited by tonicity) and solubility (aqueous solution vs. suspension)
- Viscosity (increased contact time)
### Routes of Administration: Topical - Drops

- **Lipid solubility:** lipid-rich epithelial cell membrane vs. water-rich stroma
- **pH and ionic charge:** Most eye drops are weak bases, existing in both charged and uncharged forms, enhancing absorption.

### Routes of Administration: Topical - Drops

- **Surfactants:** preservatives are surface-active agents that alter cell membranes in the cornea and bacteria, increasing drug permeability and preventing bacterial contamination.

### Routes of Administration: Topical - Drops

- **Reflex tearing:** Ocular irritation and secondary tearing wash out of the drug reservoir in the tears and reduce contact time with cornea, especially when drops are not isotonic, have non-physiological pH, or contain irritants.

### Routes of Administration: Topical - Drops

- **Tissue binding:** proteins in the tears and on the ocular surface may bind drug making the drug unavailable or creating a slow release reservoir. This may affect peak effect, duration of action, and delayed local toxicity.

### Routes of Administration: Topical - Drops

- **Increases contact time of drug with ocular surface;**
- **Mixture of petrolatum and mineral oil;**
- **Water-soluble drugs are insolvent in the ointment and are present as microcrystals.**
- **The surface microcrystals dissolve in the tears; the rest are trapped until the ointment melts.**

### Routes of Administration: Topical - Oint.

- Only drugs with high lipid solubility and some water solubility will get into both tears and corneal epithelium.

### Routes of Administration: Peri-ocular Injections

- **Subconjunctival, subTenon’s, peribulbar, and retrobulbar;**
- **Allow drugs to bypass the conjunctival/corneal epithelial barrier and reach therapeutic levels in the posterior segment;**
- **e.g., anesthetic agents, steroids**

### Routes of Administration: Intra-ocular Injections

- **Allow instant drug delivery at therapeutic concentrations to target site;**
- **Intracameral, e.g., antibiotics, viscoelastics, miochol;**
- **Intravitreous, e.g., triamcinolone, Avastin, Lucentis**

### Routes of Administration: Systemic

- **Extent of drug bound to plasma proteins also affects access of drug into eye - only unbound form can pass blood-ocular barrier.**
- **Bolus administration exceeds the capacity of a drug to bind to plasma proteins and so leads to higher intraocular drug levels than with slow IV drip**
Routes of Administration: Sustained Release

Devices available for delivery of steroids, gancyclovir within vitreous cavity

Sustained Release Devices

- These devices deliver an adequate supply of medication at a steady-state level
- e.g.,
  - Ocusert delivering pilocarpine
  - Timoptic XE delivering timolol
  - Ganciclovir sustained-release intracocular device
  - Collagen shields

Routes of Administration: Topical - Drops

- One drop = 50 µl
- Volume of conjunctival cul-de-sac 7-10 µl
- To increase drop absorption:
  - wait 5-10 minutes between drops
  - compress lacrimal sac
  - keep lids closed for 5 minutes after instillation

MYDRIASIS

[Gr., μυδριασις]
Dilation of the pupil

Dilating Agents

- Dependent on iris pigmentation
- Mechanism: Inhibition of iris constrictor and ciliary muscles

MYDRIASIS

- Blockage of cholinergic stimulation to sphincter ms. of iris, ciliary body
- Stimulation of iris dilator ms.

CYCLOPLEGIA

[Gr. κυκλος = circle, + πληγη = blow, stroke]
Paralysis of accommodation (ciliary ms.)

CYCLOPLEGIC AGENTS

- Atropine (0.5%, 1%)
- Homatropine (1%, 5%)
- Scopolamine (Hyoscine)
- Cyclopentolate (0.5, 1, 2%)
- Tropicamide (0.5, 1%)
**Parasympatholytic Drugs**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mydriasis Onset</th>
<th>Cycloplegia Onset</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atropine</td>
<td>30 min.</td>
<td>60 min.</td>
<td>10 – 14 days</td>
</tr>
<tr>
<td>Homatropine</td>
<td>10 – 30 min.</td>
<td>30 – 90 min.</td>
<td>2 – 4 days</td>
</tr>
<tr>
<td>Scopolamine</td>
<td>40 min.</td>
<td>40 min.</td>
<td>2 – 6 days</td>
</tr>
<tr>
<td>Cyclopentolate</td>
<td>20 – 30 min.</td>
<td>15 – 45 min.</td>
<td>12 – 24 hrs</td>
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**CYCLOPENTOLATE HCl**

- **Available as**
  - Cyclogyl
  - Ak-Pentolate, inter alia
- **Chemistry**
  - Anticholinergic
  - Parasympatholytic
- **Action**
  - **Mydriasis**
    - Onset: 15 – 30 minutes
    - Duration: 24 hours
  - **Cycloplegia**
    - Onset: 15 – 45 minutes
    - Duration: 24 hours

**CYCLOPENTOLATE HCl**

- **Toxicity**
  - Facial flushing
  - Wandering, irrelevant speech
  - Disorientation, hallucinations
  - Psychosis
  - Ataxia, restlessness
  - Grand mal seizures

**CYCLOPENTOLATE HCl**

- **Side Effects**
  - Irritation with concentration
  - ↑ IOP in open angle glaucoma
  - Angle closure glaucoma

**CYCLOPENTOLATE HCl**

- **Guidelines**
  - Use lowest concentration
  - Avoid repetition
  - Avoid seizure-prone infants, elderly
  - Use punctal occlusion

**TROPICAMIDE**

- **Chemistry**
  - Anticholinergic
  - Parasympatholytic

**Allergy**

- Irritation, injection
- Lacrimation, mucoid discharge
- Atopic dermatitis
TROPICAMIDE

- Available as
  - Mydriacyl
  - Tropicacyl, inter alia
- 0.5%, 1.0% collyrium

Action
- Mydriasis
  - Onset 15-30 min.
  - Duration 4-6 hours
- Cycloplegia
  - Onset 20-30 min.
  - Duration 4-6 hours

Side Effects
- Irritation on instillation
- ↑ IOP in open angle glaucoma
- Angle closure glaucoma
- Better mydriatic than cycloplegic

Toxicity
- Rare, due to brief action
- Cyanosis
- Muscle rigidity
- Vasomotor instability

PHENYLEPHRINE

- Available as
  - NeoSympheine
  - Ak-Dilate
  - Mydfrin
  - Efricel, inter alia
- 2.5%, 10% collyria

Chemistry: α₁ adrenergic stimulator, agonist (radial iris fibers)

Action:
- Mydriasis
  - Onset: 10-20 min.
  - Duration: ~ 3°
- Vasoconstriction

Clinical Effects
- Rapid onset
- Virtual absence of cycloplegia
- Accentuates effect of mydriatic

Side Effects
- Irritation on instillation
- Angle closure glaucoma

Other Actions:
- Reduced aqueous inflow
- Reduced resistance to outflow
- Stimulation of dilator ms.
PHENYLEPHRINE
Toxicity
• 1 gtt. 10% coll. = 3.3-6.7 mg.
• Enhanced absorption in inflamed eyes

PHENYLEPHRINE
Guidelines
• Use punctal occlusion
• Do not use in patients on MAO inhibitors or tricyclic antidepressants (e.g., Parnate, Tofranil, Elavil, Sinequan).

PHENYLEPHRINE
Guidelines
• Use cautiously in hypertension, cardiac disease, aneurysm
• Use 2.5% coll. in infants, elderly
• Approximately gtt.1/eye/hour

DAPIPRAZOLE
Trade Name
Rev-Eyes®

DAPIPRAZOLE
[Rev-Eyes]
• C_{19}N_{27}N_{5}HCl
• M.W. 361.93

DAPIPRAZOLE
Description
α-adrenergic blocking agent

DAPIPRAZOLE
Pharmacology
• α-adrenergic smooth muscle blocker
• Induces miosis by dilator muscles
DAPIPRAZOLE
Pharmacology
• No action on ciliary ms.
• Minimal effect on sphincter ms.

DAPIPRAZOLE
Indications
• Iatrogenic mydriasis by adrenergic (or parasympatholytic) agents

DAPIPRAZOLE
Dosage
• Reconstituted as 0.5% collyrium
• gtts ii O.U.; repeat after 5 min.

DAPIPRAZOLE
Pregnancy
• Safety in pregnancy, nursing not established
• Not embryocidal, teratogenic in rats, rabbits

DAPIPRAZOLE
Pediatrics
• Safety and efficacy not established

DAPIPRAZOLE
Contraindications
• Hypersensitivity
• Strong parasympatholytic agents
• Use only once/week/pt.

TOPICAL ANESTHETICS
Mechanism of Action:
• Reversible block, competitive inhibition of ACh
• Decreased membrane permeability to Na⁺ flux

TOPICAL ANESTHETICS
Proparacaine (Alcaine, Ophthetic, Fluoracaine, inter alia)
Benoxinate (Fluress)
Tetracaine
Cocaine (1% - 4% as anesthetic)

PROPARACAINE
• Available as
  - Ophthaine
  - Aphihetic
  - Ak-taine
  - Alcaine
• 0.5%
TOPICAL ANESTHETICS

- Onset: 5-30 sec.
- Duration:
  - Varies with concentration, frequency of instillation
  - Generally, 20-30 min.

TOPICAL ANESTHETICS Side Effects

- Stinging on instillation
- Suppression of reflex blinking
- Increased corneal permeability to drugs

TOPICAL ANESTHETICS Maximum Effective Concentrations

- Proparacaine 0.5%
- Tetracaine 1%
- Lidocaine 4%
- Cocaine 20%
- Benoxinate 0.4%

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TOPICAL ANESTHETICS Epithelial Toxicity

- Minimal: Lidocaine (2-4%)
- Maximal: Cocaine (4-20%)

TOPICAL ANESTHETICS Toxicity

- Epithelial punctate keratopathy
- Retardation of epithelial healing
- Idiosyncrasy
- Allergy: exfoliative dermatitis

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PROPARACAINE

- Onset: 5-20 sec. (ave. ~13 sec.)
- Duration: 15-25 min.
- Irritation: minimal

PROPARACAINE

- Allergy
  - Rare;
  - No cross-reaction with tetracaine, benoxinate

PROPARACAINE

- Toxicity
  - Punctate epithelial keratopathy
  - Stromal edema (after 5-10 min.)
  - Suppression of reflex blink; drying
  - Suppression of epithelial regeneration

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  - Suppression of epithelial regeneration

Fluorescein – Topical

- Available as drops or strips
- Uses: stain corneal defects and abrasions, applanation tonometry, detecting wound leak, NLD obstruction
- Caution:
  - Stains soft contact lens
  - Fluorescein drops can be contaminated by Pseudomonas sp.
ROSE BENGAL
ÅStains devitalized epithelium
ÅUses: Severe dry eye, herpetic keratitis

GLYCERIN, USP
Glycerol
ÅChemistry: Trihydric Alcohol (CH₂OHCHOCH₂OH)
ÅColorless viscous liquid
ÅMiscible with H₂O, EtOH
ÅUsed in 50-75% conc. (aqueous)

GLYCERIN
ÅAction: Osmotic agent
- Hydroscopic
- Deturgesces corneal edema
ÅOnset: 1-2 min.

GLYCERIN
Side Effects
ÅBurning pain on instillation
ÅTransient action (topical)

GLYCERIN
Toxicity
Rare, topically

GLYCERIN
Advantages
ÅInexpensive
ÅUse as gonioscopic lubricant