Adverse reactions to ocular drug therapy

Senior Lecturer Jay Meyer
Professor Charles McGhee
Department of Ophthalmology

Ophthalmic Medications

- How many drops should be used per dose?
- How can you reduce the systemic effect of drops?
- Minimum time between instillation of two different drops to prevent major washout?
- What is the most likely reason a glaucoma drop is ineffective?

Route of penetration

Topical drugs – route of penetration

1. Cornea
2. Conjunctiva
3. Sclera

Practical aspects of topical ocular medication: Cul de sac & tear film

The cul de sac & tear film compartment

Normally 7-10 μl volume

Expands transiently to 30 μl

However, topical drop size typically 40-70 μl

Elimination of Drug from the eye

Initial overflow and loss
1. Cul de sac expands transiently to 30 microlitres
2. Average ophthalmic drop approx. 50 microlitres

Therefore excess volume of drug:

a) drains via naso-lacrimal duct within 15 seconds
b) or overflows lid margin onto cheek
Elimination – naso-lacrimal flow

Approximately 80% of the applied drop leaves via naso-lacrimal system without entering the eye! 2-3 rather than a single drop does not increase ocular dose but does increase systemic dose.

Local toxicity from topical ocular agents

Anaesthetics
Neomycin
Preservatives

Systemic toxicity of topical ocular drugs

Topical beta-blockers:
- Respiratory and cardiac depression
- Asthma exacerbation

Topical Atropine:
- Fatal adult dose is 100mg, however, for 4Kg baby, dose is 10mg or 20 drops of 1%

G Timolol (0.25 - 0.50%)
- Foreign body sensation
- Dry eye symptoms
- Decreased corneal sensitivity
- Hypersensitivity to components
- Pseudopemphigoid
- Ptosis

Systemic side effects
- Cardiovascular
  - Bradycardia
  - Atrialfthmia
  - Heart block
  - Hypotension
  - Worsening angina
  - Impotence
**G Timolol (0.25 - 0.50%)**

**Systemic side effects**
- Respiratory
  - Worsening asthma
  - Bronchospasm
  - Dyspnoea
  - Respiratory failure

**G Timolol (0.25 - 0.50%)**

**Systemic side effects**
- Central nervous system
  - Insomnia
  - Depression
  - Nightmares
  - Confusion
  - Paraesthesia

**G Atropine 1%**

- Extreme care with children
- Remember 1% drop = 10mg/ml of drug
- Therefore 10 drops (50μm) = 5mg

**Allergic conjunctivitis with lid involvement (atropine)**

**Prostaglandin analogues (Latanoprost, Bimatoprost, Travoprost)**

- 5-15% of patients have adverse events
- Burning & Stinging
- Hyperaemia (redness)
- FB sensation
- Punctate epitheliopathy

**Prostaglandin analogues**

- Increased eyelash length & thickness
- Iris pigmentation
- Iritis / uveitis
- Cystoid macular oedema
- Reactivation of HSV
Prostaglandin Analogues

- Ocular side effects
  - H - hypertrichosis
  - I - iris pigmentation
  - C - conjunctival injection
  - C - CME (esp. if posterior capsule broken)
  - U - uveitis (↓ blood aqueous barrier)
  - P - pseudodendrites & HSK exacerbation
  - S - skin pigmentation (lid tightening/ tethering)

Increased iris pigmentation with prostaglandin analogues

Prostaglandin associated periorbitopathy

Prostaglandin eyelash growth (now marketed as Latisse)

Brimonidine 0.2%

- 10-20% adverse events
- Allergic follicular conjunctivitis
- Hyperaemia
- Burning sensation
- Rarely – corneal erosions
- Miosis

Follicular conjunctivitis
Brimonidine 0.2%

- Systemic effects
  - Allergic lid reaction
  - Altered taste
  - Dry mouth
  - Nasal drying
  - Hypertension
  - Fatigue

Combined medications
e.g. G. Combigan or G Cosopt

- Combined drugs
- Combined side effects

COMPLIANCE:
The Hidden Challenge Of Glaucoma Management

Rate of non-compliance?

Compliance

- Patient compliance is major issue
  - Asymptomatic
  - Long term therapy
  - Benefit of treatment not apparent
  - Several medications
  - Expense of treatment
  - Inconvenience of treatment
  - Side effects of treatment

25-58% do not use meds as prescribed
- True non compliance rate is probably at least 30%-40%

Preservatives

- BAK
  - Cytotoxic effects—cell culture + animal/ human studies
  - Mechanism of action
    - Disruption of cell wall & cytoplasmic membrane

Preservatives
Allergies

- Have to discern seasonal allergies from medication allergies
- Highest rate of allergies
  - alpha agonists
  - CAI
  - Pilocarpine

Ocular and systemic side effects

- These are relatively common with topical agents
- Take careful patient history
- Refer to data sheet before Rx

Oral Medications for MGD

- First Line Treatments:
  - Artificial Tears
  - Warm Compresses
  - Lid Scrubs/Massage
  - Omega-3 supplementation
- Oral Medications:
  - Doxycycline
  - Azithromycin

Mechanism of Action

Doxycycline
- Tetracycline antibiotic
- Anti-inflammatory
- Inhibit matrix metalloproteinases
- Antimicrobial
- Reduce bacterial lipases

Azithromycin
- Macrolide antibiotic
- Anti-inflammatory
- Inhibits cytokines, MMPs, chemokines
- Antimicrobial
- Long half life

Dosing

- **Azithromycin**
  - 500mg once, then 250mg daily for 4 days
  - Or, 1 gram weekly for 3 weeks

- **Doxycycline**
  - 50-100mg daily for 1 month

Contraindications

- **Doxycycline**: Contraindicated during pregnancy and ≤8 years
- **Azithromycin**: FDA black box warning for fatal heart rhythm. Most likely if prolonged QT interval, on medications for arrhythmia, electrolyte imbalances
- Pregnancy: FDA category B—no human studies, animal studies no evidence of harm; Use during pregnancy only if clearly needed.
**Side Effects**

**Doxycycline**
- Photosensitization
- GI upset, diarrhoea
- Vaginitis

**Azithromycin**
- Decreased appetite
- GI upset, diarrhoea
- Vaginitis

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**Adverse ocular reactions to systemic drug therapy**

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**Eye Drops:**

**systemic side effects**

- **Adverse Drug Events**
  - > 2 million hospital visits
  - > 100,000 deaths

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**Background**

- OTC medicines 40% >60 year olds
- Prescription medicines

**Likelihood of side effects depends on:**
- Prevalence of the treated condition
  - eg. Hypertension vs malaria
- Prescribing habits
- Therapeutic index (lethal vs effective dose)

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**Types of ocular effects**

- Cyclospasm
- Cycloplegia
- Media changes
- Optic neuritis
- Retinal changes
- Central effects

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**Common ocular effects**

- Cataract
- ↓ accommodation
  - +/- mydriasis
- ↑ IOP
**Corticosteroids: established SE.**

- Steroid induced glaucoma/hypertension
- Posterior sub-capsular cataract
- Increased risk of infections
- Central serous retinopathy

**Rx Routes**
- Oral
- Inhaled
- Applied to skin

**Alimentary tract**

*post-op nausea/vomiting, travel sickness*

- Drugs act locally in the gut & do not require absorption for intended effect
- Examples:
  - Hyoscine (Buscopan)
  - Muscarinic Acetyl Choline antagonist
- Ocular side effects:
  - Mydriasis
  - Cycloplegia (mild & transient)
  - Acute angle closure

**Retinal Toxicity**

- Interferon: retinal hemorrhages, CWS
- Niacin: macular oedema
- Thioridazine: “salt and pepper” retinopathy

**Bull’s Eye Maculopathy**
Plaquenil/Hydroxychloroquine toxicity

Cardiovascular system
- Direct ocular effect
- Indirect effect – BP & blood flow
- Cardiotoxic eg Digoxin
  - Toxic effect on Retina
  - Glare / photopsia
  - Digoxin-mediated inhibition of Na/K ATPase influences normal uptake of extracellular potassium by Muller’s cells and other retinal neurons – may result in decreased color vision.

Cardiovascular/Renal systems
- β-blockers
  - Oculo-mucocutaneous syndrome
  - Similar to:
    - Stevens-Johnson Syndrome
    - Sulphonamides

Cardiovascular system
- Anti-arrhythmics eg Amiodarone
  - Vortex keratopathy (verticillata)
  - Optic neuropathy

Respiratory system
- Treatment usually local (inhalers)
- Limited side effects
Examples
- Ventolin (Salbutamol)
  - Mydriasis
  - Tachycardia
Central Nervous system
- Affects ocular tissue or brain centres controlling eye movements

Examples
- Hypnotics eg benzodiazepines
  - Blurred vision
  - Reduced accommodation
  - Abnormal extra ocular muscle movement

Central Nervous System
- Antipsychotics eg Chlorpromazine
  - Pigmentary deposits (lens, iris, Descemet's membrane)
  - Corneal deposits

- Anticonvulsants
  - Nystagmus & diplopia (overdose)

30 y/o female eye pain, blurry vision
- Central nervous system
  - Topiramate
    - Choroidal effusions
    - Myopic shift
    - Elevated IOP

Infectious Diseases
- Antibiotics eg Tetracycline
  - Transient myopia
  - Colour vision defects
  - Stains soft CL

- Anti-tuberculosis eg Ethambutol, Isoniazid
  - Toxic optic neuropathy

Blepharitis
- Azithromycin
  - FDA black Box warning:
    - Potentially fatal irregular heart rhythm

- Doxycycline
  - Pregnancy class D—use not recommended unless essential for patients welfare
Optic neuropathy

<table>
<thead>
<tr>
<th>Drug</th>
<th>Optic Neuropathy</th>
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<tbody>
<tr>
<td>Methadone</td>
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<tr>
<td>Niacin</td>
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<td>Dexamethasone</td>
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<tr>
<td>Oxymetazoline</td>
<td>Optic neuropathy</td>
</tr>
<tr>
<td>Isopropyl alcohol</td>
<td>Optic neuropathy</td>
</tr>
<tr>
<td>Verapamil</td>
<td>Optic neuropathy</td>
</tr>
</tbody>
</table>

Source: Reference 1

Endocrine system

- Corticosteroids
  - Cataract (posterior subcapsular)
  - Raised intraocular pressure
  - Corneal thinning

Endocrine System

- Zolendronate: Bisphosphonate to treat osteopenia.
  - Acute Anterior Uveitis
    - 8 of 1001 subjects developed uveitis!

Viagra (Sildenafil citrate)

- Pharmacology
  - Inhibits vascular-associated enzyme phosphodiesterase 5 (PDE5)
  - Lesser but definite inhibitory effect on PDE6, located in the retina

Viagra (Sildenafil citrate)

- Ocular effects
  - Transient, mild impairment of color discrimination (blue-green spectrum) at peak plasma levels
  - No significant effects on IOP
  - Possible association with NAION

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Thanks!