Complications of Pharmaceuticals Every Optometrist Should Know!

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Heart of America
February 11, 2022

Disclosures
- The content of this activity was prepared independently by Dr. Caldwell
- Lectured for: Alcon, Allergan, Aerie, BioTissue, Kala, Maculogix, Ophirane, RVL, Henu
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Thoughts
- Always check the medication list
- Review it with the patient (techs don’t always update)
- Medications to H.A.T.E in neuro-op (Andy Lee, MD)
  - Hydroxychloroquine / chloroquine retinopathy
  - Amiodarone optic neuropathy - Anterior ischemic optic neuropathy
  - Tetracycline: pseudotumor cerebri
  - Tiambutol optic neuropathy
  - The erectile dysfunction agents (Viagra) - Anterior ischemic optic neuropathy

Antibiotics
- Fluoroquinolones
  - Levaquin™ (levofloxacin)
  - Cipro™ (ciprofloxacin)
  - Tendon rupture
  - Retinal detachment
    - 1 in 2,500 will experience (compared to 1 in 1,000 who will experience tendinitis)
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PTC VS. IIH (THANKS DR. JOE SOWKA)
- Pseudotumor Cerebri (PTC)
  - Increased intracranial pressure in the absence of an intracranial mass lesion
  - Many causative agents have been identified
- Idiopathic Intracranial Hypertension (IIH)
  - Increased intracranial pressure without an identifiable cause
  - Young, obese females are at risk
- Primary PTC
  - IIH
  - Poor CFS drainage
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Alpha 1 Blockers
- Floppy iris syndrome
- Treatment of enlarged prostate:
  - Uroxatrol™ (Alfuzosin)
  - Flomax™ (Tamsulosin)
    - These two agents LIKELY have the highest incidence of causing floppy iris syndrome, as they are selective for alpha 1a receptors, which are also predominant in the eye.
- Treatment of CHF and/or hypertension
  - Coreg™ (Carvedilol)
    - Alpha1/beta 2 blocker
  - Hytrin™ (Terazosin)
    - Alpha 1 blocker

Anti-arrhythmics
- Treatment of cardiac arrhythmia
  - Cordarone™ (amiodarone)
    - Corneal deposits
    - Optic neuritis

65-year-old woman
- Patient reports decreasing vision over past 6-9 months. Especially at near
- Vision 20/50 OU

Stages
Grade I: Punctate opacities in a horizontal linear pattern in the inferior cornea
Grade II: More aligned deposits in a linear pattern that extend into the inferior pupillary margin toward the limbus
Grade III: Increased numbers of branching patterns in the inferior pupillary area into the visual axis
Grade IV: Deposits form additional clumps compared with grade II

Topography
67-year-old man complains of vision slowly deteriorating over the past 8 months

- History of NA-ION 10 months ago OD
- Patient sees family physician for physical due to recent NA-ION
- Patient has not been to PCP for 35 years
- Patient started Cardarone™
- VA 20/80 OD 20/25 OS (9 months ago)
- VA 20/400 OD 20/200 OS (today)
- CF: severe constriction OU
- SLE: vortex corneal whorls OU
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Amiodarone Optic Neuropathy
(Toxic Optic Neuropathy)

Rhopressa™ 0.02%
(netarsudil ophthalmic solution)

Aerie Pharmaceuticals
- Approved December 2017
- Treatment of glaucoma or ocular hypertension
- Rho kinase inhibitor (ROCK-1 inhibitor)
- Once daily in the evening
- Twice a day dosing is not well tolerated and is not recommended
- Side Effects
  - Conjunctival hyperemia
  - Corneal verticillata
  - Conjunctival hemorrhage

Rhopressa™ 0.02% (netarsudil)
Causes Expansion of TM in Donor Eyes
Increases TM Outflow Facility in Clinic

TM: Trabecular Meshwork
SC: Schlemm's Canal
Control: buffered saline solution
ESV: Episcleral Vein


Netarsudil is Similarly Effective at Baseline IOPs
<25 mmHg and ≥25 mmHg
Pooled Analysis Rocket 1, Rocket 2, Rocket 4

Day 90: Change from Baseline IOP by Baseline Subgroup (Pooled)

Rhopressa™ 0.02%
- No labeled contraindications for Rhopressa™
- No clinically relevant effects on vital signs
  - Blood Pressure
  - Heart Rate

No changes were generally small and not clinically relevant in both groups

TM Outflow Facility
Healthy volunteers

No changes were generally small and not clinically relevant in both groups

Netarsudil is Similarly Effective at Baseline IOPs
<25 mmHg and ≥25 mmHg
Pooled Analysis Rocket 1, Rocket 2, Rocket 4

Day 90: Change from Baseline IOP by Baseline Subgroup (Pooled)

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**Conjunctival Hemorrhage was Sporadic and Severity did not Increase with Continued Dosing**

<table>
<thead>
<tr>
<th>Medication</th>
<th>QD (n=79)</th>
<th>Twice Daily (n=75)</th>
</tr>
</thead>
<tbody>
<tr>
<td>New</td>
<td></td>
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<tr>
<td>9146</td>
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<tr>
<td>Greg</td>
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</tbody>
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**Cornea Verticillata Due to Phospholipidosis**

Medications known to cause verticillata, amiodarone, chloramphenicol, naproxen, phenothiazine, ocular gentamicin and tobramycin.

*Raizman MB

**Cornea Verticillata Due to Phospholipidosis**

Due to phospholipidosis where the parent drug is complexed with phospholipids in the lysosomes.

**My Experience**

OO treated Q5 gm

**Summary of the Most Common Netarsudil Ocular TEAEs**

<table>
<thead>
<tr>
<th>Conjunctival Hypersensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>54.4% TEAE</td>
</tr>
<tr>
<td>Severity did not increase with continued dosing</td>
</tr>
<tr>
<td>Sporadic</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Conjunctival Hypersensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>20.0% TEAE</td>
</tr>
<tr>
<td>Asymptomatic</td>
</tr>
<tr>
<td>7.9% experiencd reduced visual acuity (not clear to a directly assessed), all resolved after 13 weeks of D/S</td>
</tr>
</tbody>
</table>

**Clinical Pearl:** When you encounter a pt with these pharmaceuticals, consider and evaluate for toxic optic neuropathy (TON)
Ethambutol

- Toxic optic neuropathy
- 2 cases in the past 12 months (2019)

81-year-old woman

- Calls the office reporting decreased vision (3/13-19)
- Was warned vision could decrease due her medications
- Glaucoma patient
- Mycobacterium avium infection
- Ethambutol, rifampin, and azithromycin
- Ethambutol started October 2017
- Glaucoma patient
- Was on latanoprost and Rhopressa
- Had KDB
  - No glaucoma drops currently

3/13/19 20/30, 20/100, 20/25

4/29/19 20/25, 20/50, 20/20

7/29/19 20/20, 20/25, 20/20

Progression
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Osteoporosis Medications
- Bisphosphonates:
  - Fosamax™ (Alendronate)
  - Actonel™ (Risedronate)
  - Epidetids
  - Uveitis
  - Iritis
- Typically, the benefit of using these agents outweigh the risks for ocular side effects
- Encourage patients to get regular ophthalmic exams and to report any acute changes!

COX-2 Specific Inhibitors
- Celebrex™ (celecoxib)
  - Cataracts
  - Glaucoma
  - Conjunctival hemorrhage
  - Vitreous floaters
- Hey Celebrex™, where did your brothers Vioxx™ and Bextra™ go?!? Oh how we miss them...

Anticonvulsants
- Sabril™ (vigabatrin)
  - Uncommon agent used in infantile spasms and in refractory partial complex seizures
  - FDA mandated BLACK BOX WARNING:
    - Optic atrophy
    - Optic neuritis
    - Peripheral constriction of visual field
    - Decrease in visual acuity

Sabril™ (vigabatrin)
- Toxic Optic Neuropathy
- Selective, irreversible, inhibitor of GABA transaminase for refractory complex partial seizures and infantile spasms
- Clearly been shown to cause a dose-dependent, permanent peripheral field constriction.
- The earliest reports of toxicity were after 11 months of exposure
  - The vision loss is usually asymptomatic and spares the macula
  - Sub-clinical depression of macular function and color vision deficits have been reported
  - Mechanism has not yet been fully demonstrated
  - Most likely involves toxicity to both retinal photoreceptors and ganglion cells
  - Possibly induces a taurine deficiency that leads to toxicity
  - Taurine supplementation may prevent toxicity

Autoimmune Agents
- Treatment of Multiple Sclerosis
  - Gilenya™ (fingolimod)
    - FDA-approved oral agent for the treatment of relapsing forms of multiple sclerosis (MS) in September 2010
    - Macular edema
      - FAME - Fingolimod-Associated Macular Edema

52-year-old woman
- History of MS was switched from Tyabrili™(natalizumab) to Gilenya™ (fingolimod)
- Blurred vision in her left eye, BVA 20/40
  - Noticed blurred vision 7-8 weeks after starting Gilenya™
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Gilenya™ (fingolimod) & FAME
- Prior to starting medication
  - Follow up in 3-6 months after medication started
- Be aware of FAME
- If FAME occurs
  - Stopping Gilenya typically will reverse edema
  - May need topical NSAID and/or steroid

Another Gilenya™(fingolimod) and FAME

After D/C Gilenya™(fingolimod)

Autoimmune Agents
- Treatment of rheumatologic conditions
  - Rheumatoid arthritis, systemic lupus erythematos
- Plaquenil™ (hydroxychloroquine)
  - Bull’s eye maculopathy

Immunosuppressive Medications
- Disease-Modifying Anti-Rheumatic Drugs (DMARDs)
  - Traditional Meds and Biologics
    - Methotrexate +/-
    - Hydroxychloroquine (Plaquenil™)
    - Tumor Necrosis Factor α inhibitors
      - Adalimumab (Humira™)
      - Infliximab (Remicade™)
      - Etanercept (Enbrel™)
      - Certolizumab (Cimzia™)
  - Additional Agents
    - Abatacept (Orencia™)
    - Tocilizumab (Actemra™)
    - Tofacitinib (Xeljanz™)
    - Rituximab (Rituxan™)

Plaquenil™
- Hydroxychloroquine (Plaquenil™) - Anti-malarial
  - Ophthalmic side effects (infrequent with current dosing ranges):
    - Irreversible retinal damage has been observed (“chloroquine retinopathy”).
    - If there are any indications of abnormality in the color vision, visual acuity, visual field, or retinal macular areas, or any visual symptoms (eg, light flashes or streaks), d/c drug stat
Revised Recommendations on Screening for Chloroquine and Hydroxychloroquine Retinopathy

- Recommendations were 2002 by the American Academy of Ophthalmology
- Improved screening tools and new knowledge about prevalence of toxicity have prompted change
- The plan of a joint review by clinical experts is under way
- There is no agreed-upon treatment for this condition
- Screening for the earliest signs of functional or anatomic change
- Plaquenil toxicity is not well understood

- Risk of Toxicity: The risk of toxicity is dependent on daily dose and duration of use. At recommended doses, toxicity is unlikely. At higher doses, toxicity can occur. At any dose, toxicity can occur, especially in patients with pre-existing retinal or optic nerve disease.

- Major Risk Factors: High doses and long duration of use are the most significant risks. Other major factors include age, race, and history of retinal or optic nerve disease.

- Pattern of Retinopathy: The primary pattern of retinopathy is parafoveal. Asian patients often show an extramacular pattern of damage. In addition, vision loss may occur in patients with pre-existing retinal or optic nerve disease.

- Dose: The risk of toxicity is dependent on daily dose and duration of use. At recommended doses (2002), the risk of toxicity is under 1% for up to 5 years. The risk is under 2% for up to 10 years. The risk rises to almost 20% after 20 years.

- Counseling: Patients (and prescribing physicians) should be informed about risk of toxicity, proper dose, and the importance of regular annual screening.

- American Academy of Ophthalmology recommendations on screening for chloroquine (CQ) and hydroxychloroquine (HCQ) retinopathy are under review. New information about the prevalence of toxicity has prompted change. The plan of a joint review by clinical experts is under way. There is no agreed-upon treatment for this condition. Screening for the earliest signs of functional or anatomic change is important to prevent central visual loss. However, questionable test results should be repeated or reinterpreted.

- Retinopathy (2016 Revision)

- American Academy of Ophthalmology Statement

- Published by Elsevier Inc.

- ISSN 0161-6420/16

- http://dx.doi.org/10.1016/j.ophtha.2016.01.058

- The primary screening tests are automated visual field (VF) plus spectral-domain optical coherence tomography (SD-OCT) of the macula and peripapillary retinal nerve fiber layer (pPRLNFL). Modern screening should detect retinopathy before it is visible in the fundus. Improved screening tools and new knowledge about the prevalence of toxicity have prompted change.

- The American Academy of Ophthalmology recommendations on screening for chloroquine (CQ) and hydroxychloroquine (HCQ) retinopathy are under review. New information about the prevalence of toxicity has prompted change. The plan of a joint review by clinical experts is under way. There is no agreed-upon treatment for this condition. Screening for the earliest signs of functional or anatomic change is important to prevent central visual loss. However, questionable test results should be repeated or reinterpreted.
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Plaquenil Toxicity

Plaquenil Toxicity

Antivirals

What is different about the oral antivirals?

- Main reason for early discontinuation of oral acyclovir in HEDS
- Gastrointestinal side effects
- Rash

Many patients on oral acyclovir have GI symptoms
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Acyclovir vs. Valacyclovir vs. Famciclovir
What is the difference?

Acyclovir
- Zovirax® contains lactose presence or absence of lactose in generic acyclovir varies
- Presence or absence of lactose in generic acyclovir varies
- Zovirax® and all generics are free of lactose
- Generics available in the US contain lactose
- * In Europe you can get generic famciclovir without lactose (Teva Pharmaceuticals, Israel)

Valacyclovir
- Valtrex® and all generics are free of lactose
- Generics available in the US contain lactose
- * In Europe you can get generic famciclovir without lactose (Teva Pharmaceuticals, Israel)

Famciclovir
- Acyclovir and valacyclovir are better tolerated than famciclovir
- Acyclovir and valacyclovir have fewer side effects than famciclovir
- Famciclovir has a higher risk of CNS adverse effects in the elderly: agitation, hallucinations, confusion
- Clinical Take Home Point:
  - Consider famciclovir in elderly patients who CNS side effects with acyclovir or valacyclovir
  - Other major concern with elderly patients is age-related reduced kidney function

CNS Effects in Elderly Patients

Questions?

Thank You!
Tracy and Greg