Course #

153

Pill Problems:
Ocular Complications From Systemic Meds
PILL PROBLEMS:
OCULAR COMPLICATIONS FROM SYSTEMIC MEDICATIONS

Course description: Optometrists are well aware of the potential systemic complications that can occur with the drugs prescribed for ocular disorders. Less well known however are the ocular manifestations that can arise from the use of various systemic medications, such as antihistamines, anti-inflammatory agents and cardiac medications. This course reviews some of the more common oral prescription medications and their ocular complications, through the use of case examples and series culled from the current literature.

• Common Drugs with Ocular Complications
  – Alendronate
  – Amiodarone
  – Benztropine
  – Diphenhydramine
  – Hydroxychloroquine
  – Sildenafil
  – Tamsulosin
  – Tetracycline
  – Topiramate
  – Warfarin

• DIPHENHYDRAMINE
  – Trade: Benadryl®, numerous generic
  – Drug class: non-selective histamine blocker
    ▪ Ingredient in numerous cold medications and sleep aids (e.g. Nytol®, Tylenol® PM)
  – Indication(s):
    ▪ Primary: nasal & non-nasal signs and symptoms of seasonal allergy, especially allergic rhinitis
    ▪ Secondary: insomnia, vertigo, motion sickness
  – Typical dosage: 25-50 mg, q4h or PRN
  – Ocular Complications
    ▪ Dry Eye
      • Due to anticholinergic effects of the medication
      • Diminishes aqueous production via autonomic innervation to the primary lacrimal gland
      • Opposite action of Salagen® (pilocarpine)
    ▪ Can also cause dry mouth, urinary retention and constipation
- Dose-dependent effect
- Reversible

  - ... to evaluate the safety of olopatadine 0.2% in a population of patients with both allergic conjunctivitis and dry eye.
  - 52 patients with ocular allergy and mild-to-moderate dry eye were evaluated.
  - Randomized to either olopatadine hydrochloride 0.2% or a tear saline once-daily for 1 week.
  - Evaluated TBUT, corneal and conjunctival staining, fluorophotometry, Schirmer's test, injection, and symptom evaluations.
  - No significant differences between the treatment groups were observed ($p > 0.05$).
  - **Conclusion:** As there were no significant changes in the signs & symptoms of dry eye, olopatadine 0.2% is safe to use in ocular allergy patients with mild-to-moderate dry eye.

- Other Manifestations
  - Drowsiness & fatigue
  - Anticholinergic effects including dry mouth, urinary retention, and constipation
  - Potential for cardiac complications, particularly arrhythmias and tachycardia
  - Potential for recreational use/abuse

- Similar Medications with Similar Effects
  - Chlorpheniramine (Chlor-Trimeton®)
  - Brompheniramine (Dimetane®)
  - Dimenhydrinate (Dramamine®)
  - Meclizine (Bonine®)
  - Loratadine (Claritin®, Alavert®)
  - Cetirizine (Zyrtec®)

- **OTC vs. Rx Drugs:** Patients do not always equate items that they buy on store shelves with the terms “drugs” or “medications”. Practitioners and technicians must be **SPECIFIC** when screening. Checklists on intake forms work well.

- **TETRACYCLINE** and derivatives
  - Trade: Sumycin®, Tetracyn®, numerous generics
  - Drug class: Tetracycline antibiotic
  - Includes doxycycline and minocycline, among others
  - Indication(s):
    - Primary: infection by susceptible bacterial strains
      - Respiratory, skin/soft tissue, UTIs most commonly
      - Rarely a “first-line” antibiotic therapy
  -
– Secondary: immunomodulatory agent for sebaceous disorders, including rosacea and MGD
– Typical dosage: 250 mg QID or 500 mg BID
– Ocular Complications
  ▪ Scleral discoloration (minocycline)
  ▪ Pseudotumor cerebri or Idiopathic intracranial hypertension
    • 0.9 per 100,000 people in general population, including children
    • Increased risk in women aged 20-44 who are 20% or more above their ideal body weight
    • Diagnosis - based on modified Dandy criteria
      ♦ Awake and alert patient
      ♦ Signs and symptoms of increased ICP
      ♦ Absence of localized neuro exam findings, except for CN VI paresis
      ♦ Normal CSF fluid findings except for increased pressure
      ♦ Absence of deformity, displacement, and obstruction of ventricular system
      ♦ No other identifiable cause of intracranial hypertension
  ▪ Other compounds associated with PTC
    • Oral contraceptives
    • Vitamin A
    • Amiodarone
    • Glucocorticoids (withdrawal)
    • Mineralocorticoids (withdrawal)
  ▪ Other Manifestations
    • Tooth Discoloration
    • Photosensitivity

• WARFARIN
  – Trade: Coumadin®, numerous generics
  – Drug class: anticoagulant (“blood thinner”)
  – Indication(s):
    ▪ Prophylaxis and/or treatment of venous thrombosis and pulmonary embolism
    ▪ Thromboembolic complications associated with atrial fibrillation and/or cardiac valve replacement
    ▪ To reduce the risk of death, recurrent myocardial infarction, and thromboembolic events such as stroke or systemic embolization after myocardial infarction
    ▪ Hypercoagulable states
  – Typical dosage: 5-10 mg daily
  – Ocular Complications
    ▪ Subconjunctival hemorrhage
- Hyphema
- Retinal hemorrhage
- Other Manifestations
  - Bleeding and bruising - can be potentiated by a variety of drugs & other substances:
    - Antibiotics (e.g. aminoglycosides, macrolides, fluoroquinolones and tetracyclines)
    - Beta-blockers
    - Levothyroxine
    - Atorvastatin
    - Fish oil / Ω-3 / vitamin E
    - Alcoholic beverages
    - Cranberry products
    - Ginseng
    - Garlic
    - Ginko biloba
    - St. John’s wort
- Management Tips
  - Patients on warfarin therapy need to be cognizant of *everything they put in their mouths*. Medications, food, beverages... EVERYTHING!!
  - INR (International Normalized Ratio) should be performed by PCP routinely.
  - Measures the extrinsic pathway of coagulation
    - Normal: 0.8 – 1.2
    - Target range on therapy: 2.0 – 3.0
    - Dangerous: >4.0

- **AMIODARONE**
  - Trade: Cordarone®, Pacerone®, numerous generics
  - Drug class: anti-arrhythmic agent (Class III)
  - Indication: for life-threatening cardiac arrhythmias
    - hemodynamically unstable ventricular tachycardia
    - shock-resistant, recurrent ventricular fibrillation
  - Typical dosage: 200-400 mg/day
  - Ocular Complications
    - Corneal Verticillata
    - i.e. “vortex keratopathy”, “hurricane keratopathy”
      - Generally asymptomatic
      - Rarely may cause haloes or slight decrease in VA
      - Seen in ~90% of patients on amiodarone >6 mos, especially those taking >400 mg/day.
      - No management required; Self-limiting & reversible
    - **WARNING**: Vortex keratopathy can also be associated with **FABRY’S DISEASE**
      - Hereditary enzyme deficiency
      - α-Galactosidase A
located on the X-chromosome

Leads to intracellular accumulation of neutral glycosphingolipids in various organs, e.g. skin, eyes, nervous tissue, kidney and heart

Findings: angiookeratomas, pain in the hands & feet, lesions of the mouth and multiple ocular signs

- Pseudotumor cerebri or Idiopathic intracranial hypertension
- Other Manifestations
  - “Blue skin”, “blue man syndrome”
  - Long-term use; more commonly seen with lighter skin tones

**TOPIRAMATE**

- Trade: Topamax®
- Drug class: anticonvulsant
- Indication(s):
  - Primary: treatment of epilepsy and other seizure disorders
  - Secondary: prevention of migraine headaches in adults
  - Off-label: treatment of bipolar disorder, obsessive-compulsive disorder, alcoholism, smoking cessation, cocaine dependence, eating disorders, and neuropathic pain.
- Typical dosage: (adults) 100 – 400 mg daily
- Ocular Complications
  - Acute myopic shift
  - Acute angle-closure glaucoma
  - Pathological Mechanism
    - Appears to be a sulfonamide-like response
    - Swelling/congestion and forward rotation of the ciliary body
    - Ciliochoroidal effusion with forward shifting of lens-iris diaphragm
    - Induces extreme anterior chamber shallowing and angle-closure
    - Congestion of ciliary body allows lens zonules to go slack
      - Results in lens thickening; this, in addition to the forward rotation of the lens-iris diaphragm induces a myopic shift
      - Lens thickening generally does not contribute to angle closure
  - NO pupil block; NO iris bombé!
  - Cyclocongestive glaucoma
    - Normal open angle
    - Cyclocongestive angle closure
- Other Manifestations
  - Dysgeusia (taste perversion)
  - Parasthesias (numbness & tingling)
  - Fatigue
  - Difficulty with concentration, attention and memory
- Weight loss

- **TAMSULOSIN**
  - Trade: Flomax
  - Drug class: **alpha-adrenergic antagonist**
  - Indication(s):
    - Primary: signs and symptoms of benign prostatic hyperplasia (BPH)
    - Off label: urinary retention in women and those with multiple sclerosis; facilitated passage of kidney stones
  - Typical dosage: 0.4 mg once daily
  - Mechanism: works by relaxing smooth muscle at the distal portion of the urethra
  - Ocular Complications
    - IFIS - Intra-operative Floppy Iris Syndrome
    - Clinical manifestations:
      - Poor preoperative dilation
      - Iris billowing and prolapse
      - Progressive intraoperative miosis
    - Management:
      - Identify patients at risk and discontinue medication if possible
      - Use of stronger dilating agents, e.g. epinephrine and/or atropine
      - Use of Malysugin or Morcher ring
  - Other Manifestations
    - Sulfur Allergy
    - Pustular, erythematous skin eruptions with urticaria
    - Can affect any part of the body
    - May progress to Stevens-Johnson syndrome in severe cases
    - Fever, chills, body aches, or flu symptoms
    - Light headedness, dizziness, weakness, drowsiness
    - Headache
    - Nausea, diarrhea
    - Runny nose
    - Diminished ejaculate
    - Decreased sex drive, which leads us to...

- **SILDENAFIL**
  - Trade: Viagra®
  - Similar medications: tadalafil (Cialis®), vardenafil (Levitra®, Staxyn®)
  - Drug class: phosphodiesterase enzyme inhibitor (PDEI)
  - Originally studied as an anti-angina medication!
  - Indication(s):
    - Primary: treatment of erectile dysfunction
    - Secondary: symptoms of benign prostatic hyperplasia
    - Off-label: pulmonary hypertension, Raynaud's phenomenon (Revatio®)
– Typical dosage:  50 mg (not to exceed 100 mg)
– Mechanism of action (warning: GRAPHIC)
– Ocular Manifestations
  ▪ Cyanopsia (“blue vision”)
    • By affecting PDE6 in the retina, sildenafil can lead to altered color vision perception (usually a blue or green “tinge” to vision).
    • 4 out of 5 men without vascular risk factors reported this problem after taking sildenafil.
  ▪ Nonarteritic anterior ischemic optic neuropathy
– Other Manifestations
  ▪ Headache
  ▪ Stuffy nose
  ▪ Facial flushing
– Other Manifestations

• HYDROXYCHLOROQUINE
  – Trade: Plaquenil®, numerous generic
  – Drug class: aminoquinoline
    ▪ anti-malarial drug
    ▪ DMARD
  – Indication(s):
    ▪ treatment of malaria
    ▪ treatment of discoid and systemic lupus erythematosus, and rheumatoid arthritis
  – Typical dosage: 400-800 mg/day (malaria); 200-400 mg/day (lupus & RA)
  – Ocular Manifestations
    ▪ Corneal deposits
    ▪ “Bulls-eye” maculopathy
      • 66 visual fields from patients with HCQ retinal toxicity.
      • HVF changes preceded fundus changes in 60% of patients.
      • Abnormalities were more obvious on pattern deviation than the gray scale.
      • Authors recommend white stimulus 10-2 fields (vs. red-stimulus), as per AAO guidelines.
    ▪ OCT: The New Standard
♦ Focal thinning and loss of parafoveal PIL (photoreceptor integrity line)

- ERG: The Emerging Standard
- Risk factors for maculopathy
  - Maintenance dose greater than 6.5 mg/kg/d
  - 120 lb. woman: >400 mg/d
  - 200 lb. man: >600 mg/d
  - Duration of treatment: >10 years
  - Evidence of renal insufficiency or hepatic disease
  - Obesity
  - Advanced age
  - Presence of macular degeneration or dystrophy
- Other Manifestations
  - Vertigo, tinnitus, headache
  - Skin rashes and dermatitis
  - GI disturbances
  - Muscle weakness

**ALENDRONATE**
- Trade: Fosamax®, numerous generic
- Drug class: aminobiphosphonate
  - anti-resorptive agent (strengthens bones)
  - similar drugs include Actonel®, Boniva®
- Indication(s):
  - Primary: treatment or prevention of osteoporosis, treatment of Paget’s disease
  - Off label: Metastatic bone cancer, hypercalcemia, vitamin D overdose
  - Typical dosage: 5-10 mg/day (osteoporosis); 40 mg/day (Paget’s disease) X 6 months
- Ocular Manifestations
  - Non-specific conjunctivitis and/or keratitis
  - Episcleritis, scleritis, anterior uveitis
- Other Manifestations
  - Nausea, dyspepsia, acid regurgitation
  - Abdominal pain, constipation, diarrhea
  - Musculoskeletal pain
  - Hypocalcemia
  - Osteonecrosis of the jaw

**BENZTROPINE**
- Trade: Cogentin® (discontinued in US); numerous generics
- Drug class: anti-parkinsonian medication
- Possesses both anticholinergic and antihistaminic effects
- Indication(s):
  - As an adjunct in the therapy of all forms of Parkinsonism
  - For control of medication-induced movement disorders due to antipsychotic agents, e.g. chlorpromazine (Thorazine®), haloperidol (Haldol®), risperidone (Risperdal®), olanzapine (Zyprexa®), quetiapine (Seroquel®)

- Typical dosage: 1-2 mg/day

- Ocular Manifestations
  - Anticholinergic effects (think atropine!):
    - Mydriasis
    - Cycloplegia
    - Impaired accommodation
    - Transient refractive shift
  - Dry eyes
  - Esotropia / diplopia
    - Proposed mechanism: The ratio of convergence to accommodation may increase with anticholinergics due to partial block of accommodation. To see a near target in the setting of blocked accommodation, children would increase accommodative effort, resulting in increased convergence. Too much convergence may cause esotropia.

- Other Manifestations
  - MORE anticholinergic effects

- CONCLUSIONS:
  - Optometric PHYSICIANS must realize that the eye is impacted by numerous systemic diseases and drugs.
  - A working knowledge of pharmacology and common drugs is essential (especially when dealing with an adult or geriatric population).
  - Even if you don’t (or can’t) prescribe them, you have the responsibility to recognize the potential ocular impact of commonly prescribed medications.