Drug Adverse Effects: Focus on some of the most serious problems

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Disclosure
• No real or potential conflict of interest to disclose.
• No off-label, experimental or investigational use of drugs or devices will be presented.

Objectives
• At the conclusion of this presentation the attendee will be able to:
  – Describe the mechanism of select less-known drug adverse effects.
  – Develop a plan for avoiding select less-known drug adverse effects.
  – Develop a plan for treating select less-known drug adverse effects.

References
Additional References at End of Presentation

38-year-old Woman
• PMH– Migraine with aura × 20+ years
  – Otherwise well
    • Treats migraine with sumatriptan 100 mg PO plus ibuprofen 600 mg PO at HA onset with significant effect "nearly all the time"
    • HA usually L side, +photo/+phonophobia, mild nausea without vomit, "all the same"
  – Using LNG-IUS (Mirena®) for contraception
  – Takes a multivitamin daily

38-year-old Woman (continued)
• HPI
  – Recent visit with neurology due to increase in migraine frequency from 1-3 per month to 1-2 per week without alarm features
    • Patient attributes increase in HA frequency to stress of part-time graduate studies while working full-time.
38-year-old Woman
(continued)

• HPI (cont.)
  - Neurologic evaluation negative including head CT
    • Placed on a medication for HA prophylaxis 2 weeks ago
    • No HA frequency reduction noted to date

• CC today
  - Bilateral headache “with lots of pressure behind both eyes,” profound photophobia with “halos” around lights, severe nausea without vomit × 4 h
  - Had used NSAID/triptan at HA onset
    • “I am really not much better.”
    • No additional contributing history

38-year-old Woman
(continued)

• Physical examination
  - Awake, alert, oriented, answers questions with ease, appropriate grooming, hydration
    • VS+, T=99°F (37.2°C), BP 138/80 mm Hg, P=78 reg, RR=18
    • Asking for lights in room to be dimmed

• Physical examination (cont.)
  - All findings bilateral
    • Injected conjunctiva without discharge
    • Ciliary flush
    • Pupils bilateral midsize, sluggishly reactive
    • Firm eyeballs without evidence of trauma

38-year-old Woman
(continued)

• Remaining neuro exam
  - WNL × photophobia

• Remaining HEENT
  - TM, pharynx neg, neck supple, carotids WNL with brisk upstroke

• Cardiac, chest, abd negative

• Vision screen
  - 20/100 bilateral
    • Does not wear corrective lens
    • Recent eye exam, “perfectly normal”

Results of Additional Testing
Working Diagnosis
Ocular History – Critical Components

General rule – Patients suffering from more serious issues will have more subjective and objective findings indicating a more serious problem.

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is the vision affected?</td>
<td>Yes</td>
</tr>
<tr>
<td>Is the eye painful?</td>
<td>Yes</td>
</tr>
<tr>
<td>Is there photophobia?</td>
<td>Yes</td>
</tr>
<tr>
<td>Was there trauma?</td>
<td>No</td>
</tr>
<tr>
<td>Wearing contact lens?</td>
<td>No</td>
</tr>
<tr>
<td>Discharge from the eye?</td>
<td>Yes, clear</td>
</tr>
</tbody>
</table>

Now what?

• Additional HPI, PE/evaluation?
• Diagnostics?

Angle-closure (Acute) Glaucoma

• Defined
  - Acute intraocular pressure (IOP) increase
• Compared to
  - Open-angle glaucoma where IOP increases gradually with few symptoms

IOP Measurement

• 38-year-old woman
• IOP
  - 67 mm Hg right eye
  - 78 mm Hg left eye
  - NL=12–22 mm Hg

True or false?

• Whenever acute glaucoma is noted bilaterally, drug-induced angle-closure should be considered. True
  - Source: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3619311/

Topiramate-induced IOP

• Onset
  - Usually between days 1 to 49 of therapy
• Resolution
  - Rapidly after discontinuation of therapy
True or false?
The supine position should be maintained during treatment for acute angle-closure glaucoma.
   True

Wearing eye patches, covers or blindfolds is encouraged during acute angle-closure glaucoma.
False, due to pupillary dilation that can worsen IOP

Drug-induced Angle-closure Glaucoma
Implicated Medications
• Via pupillary blockade
  - Adrenergic agonists
    • Phenylephrine eye drops
  - Anticholinergics
    • Ipratropium bromide via MDI
    • Promethazine PO
  - Psychotropics with anticholinergic AE
    • SSRIs, TCAs, SNRIs

Management of Sulfa Drug-induced Angle-closure (Acute) Glaucoma
• Discontinue the offending medication
  - Often sufficient for less elevated IOP
• Emergent ophthalmologic consult
• Controlling IOP if ≥45 mm Hg
  - Topical corticosteroid, NSAIDs
  - If insufficient
    • Systemic corticosteroids
    • Mannitol
  - Source: https://emedicine.medscape.com/article/1205298

True or false?
Angle-closure glaucoma is more common in females.
   True

True or false?
Compared with the use of other antibiotics, the use of fluoroquinolones carries a nearly 4-fold increased risk of Achilles tendinopathy.
   True
Drug Adverse Effects
Margaret A. Fitzgerald, DNP, FNP-BC, NP-C, FAANP, CSP, FAAN, DCC, FNAP

The Fluoroquinolones (FQ)
- Most commonly prescribed
  - Ciprofloxacin
  - Levofloxacin
  - Moxifloxacin
- How commonly prescribed?
  - 33 million Americans take a FQ each year.
  - Approximately 10% of all US residents

FQ-associated Tendon Rupture
- Why tendon rupture?
  - Drug class' high affinity for connective tissue
- Location
  - Achilles tendon most common
    - In one study = Nearly 90%

FQ-associated Tendon Rupture (continued)
- Study
  - 11,000 patients
- Rates of FQ-associated tendinopathy
  - 2.4 incidences per 10,000 patient prescriptions for tendinitis
    - Often precedes tendon rupture
  - 1.2 incidences per 10,000 for tendon rupture
    - Source: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4080593/

Best Documented FQ-associated Tendon Rupture
- Age > 60 yrs
  - Stiffer, thinner tendons
- Concomitant systemic corticosteroid therapy
  - Particularly higher dose, > 5 d of therapy
- Presence of renal dysfunction
- History of solid organ transplantation
  - Source: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2921747/

Less Potent FQ-associated Tendon Rupture
- Diabetes mellitus
- Rheumatic disease
- Gout
- Hyperparathyroidism

True or false?
Levofloxacin has been cited as the least tenotoxic fluoroquinolone in humans.
True
FQ-associated Tendinopathy

**Clinical Presentation**
- Tendon pain
  - Usually sudden onset
    - Approx. 50% in one study of Achilles tendon rupture = No pain
- Tendon inflammation, swelling

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**When is FQ-associated tendon rupture most likely to be noted?**
- **Wide time range**
  - Within 2 hours of taking the medication
  - As long as 6 months after treatment ends
  - Median time of onset of 6 days
- **In 1st month**
  - 85% present
- **Occurring after completion of therapy**
  - Approx. 50%

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**Guidelines for Fluoroquinolone Use in Athletes**

- **Avoid fluoroquinolone use unless no alternative is available.**
  - What organism are you trying to treat?
    - **UTI** - FQ alternatives = PO TMP/SMX, nitrofurantoin, cefpodoxime
    - **Resp tract such as pneumonia** - FQ alternatives = PO doxycycline with/without amoxicillin, depending on DRSP risk
      - Source: [https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4080593/](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4080593/)

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**Guidelines for Fluoroquinolone Use in Athletes**

- Systemic corticosteroids should not be used concomitantly with FQ.
  - Most likely with COPD/asthma exacerbation
    - In COPD, consider amox. with doxy for DRSP, cephalosporin such as cefpodoxime if standard *S. pneumoniae* risk and only if antimicrobial needed.
    - Asthma flare = Usually viral origin, antimicrobial only required if concomitant pneumonia

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**Guidelines for Fluoroquinolone Use in Athletes**

- Athletes, coaches, and training staff should understand the potential risk for developing this complication.
- Close monitoring of the athlete should be undertaken for 1 month after fluoroquinolone use.
Levothyroxine Drug Interactions

- You see a 38-year-old woman with hypothyroidism who is currently taking levothyroxine 100 mcg/d with excellent adherence, stating, “I take the medicine every morning on an empty stomach with a big glass of water.”

TSH Upper Limits of Normal?

- She is feeling well.
- Results of today’s laboratory testing includes a TSH = 6.5 mIU/mL. (ULN=4 mIU/mL)

What happened?

- States 2 month hx GERD sx which she attributes to stress at work
  - Started taking an OTC “stomach medication”
  - Symptoms improved

Levothyroxine-PPI Interaction

- Mechanism of interaction
  - PPI use=Less gastric secretion
  - Result=Higher gastric pH
  - Higher gastric pH=Less levothyroxine absorption
  - End product=Rise in TSH despite continuing use of advised dose

Levothyroxine-PPI Interaction

(continued)

- Levothyroxine w PPI use
  - Recheck TSH after approximately 8 weeks of using both meds
  - Adjust levothyroxine dose as needed

35-year-old with Genetically-based Coagulopathy

- Goal INR
  - 2.5–3.5, average warfarin weekly dose=56 mg
  - INR 7 d ago=3.2
  - Today=5.6
- Denies
  - Increased leafy greens, new meds, extra warfarin doses, alcohol, etc.
35-year-old with Genetically-based Coagulopathy (continued)

- Admits to going away for the weekend and "smoking some weed, something I hardly ever do"

Warfarin-marijuana Interaction

- "Theoretically, marijuana might increase the risk of bleeding when used concomitantly with anticoagulant/antiplatelet drugs."
  - Aspirin, clopidogrel (Plavix®), nonsteroidal anti-inflammatory drugs (NSAIDs), dalteparin (Fragmin®), enoxaparin (Lovenox®), heparin, warfarin (Coumadin®), and others.

Warfarin-marijuana Interaction (continued)

- "Concomitant use with marijuana may decrease warfarin metabolism or decrease the amount of warfarin bound to plasma proteins and increase warfarin effects. In one report, smoking marijuana 2–2.5 grams in a week resulted in an increase in international normalized ratio (INR)."

Marijuana Use Drug Interaction Potential

- Potential inhibitor cytochrome P450 3A4 (CYP3A4)
  - Based on in vitro evidence
    - CYP3A4 substrates include lovastatin (Mevacor®), clarithromycin (Biaxin®), cyclosporine, diltiazem (Cardizem®), estrogens, indinavir (Crixivan®), triazolam (Halcion®), approx. ~50% Rx medications

Varicella (Chickenpox)

- Prodrome of fever, malaise, headache, and abdominal pain 1–2 days before rash
  - Source: http://www.cdc.gov/chickenpox/hcp/clinical-overview.html

Varicella (Chickenpox) (continued)

- 2–3 mm vesicles that start on trunk, appear on limbs 2–3 days later
- Nonclustered lesions at a variety of stages, including crusts

Varicella (Chickenpox) (continued)

- Source: http://www.cdc.gov/chickenpox/hcp/clinical-overview.html
Varicella (Chickenpox) (continued)

- Rash characteristics
  - Usually starts on face and trunk, then spreads to extremities
  - 250–500 pruritic lesions
  - Crusted 4–7 days after rash onset
- Source: CDC, Prevention of Varicella. MMWR. 2007;56 (No. RR-4); Arvin Clin Microb Vaccine, 5th edition

True or false?

- The use of ibuprofen during acute varicella appears to dramatically increase the risk of necrotizing fasciitis. True
  - Answer source: http://www.medsafe.govt.nz/ProfArticles/necf.htm

True or false?

- Necrotizing fasciitis has been reported with NSAID use during an outbreak of shingles. True
  - Source: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2291221/

NSAIDs in Varicella Infection

- Proposed mechanism
  - Limited study, points to prostaglandin synthesis inhibition
    - Inhibit neutrophil function including neutrophil adherence
    - Immune suppression
  - Source: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2291221/

32-year-old Man

- HPI – Recurrent vomiting with colicky abdominal pain during p 4 months
  - 3 urgent care visits in 3 wk with same CC
  - NL studies
    - Abd CT
    - Lipase
    - Amylase
    - CBC w WBC
    - Chemistries
32-year-old Man with Recurrent Vomiting

- Social history
  - Alcohol=Approx. 4 beers per week
  - Marijuana=Daily use, smoking or edible
    - Has a medical use card due to difficulty sleeping
  - Denies tobacco use or other medications

Cannabinoid Hyperemesis Syndrome (CHS)

- Characteristics
  - History of regular cannabis for any duration of time=100%
    - At least weekly, more often daily
  - Cyclic nausea and vomiting=100%
    - More likely in AM
  - Resolution of symptoms after stopping cannabis=96.8%

Cannabinoid Hyperemesis Syndrome (CHS) (continued)

- Characteristics (cont.)
  - Compulsive hot bath/shower with symptom relief=92.3%
  - Male predominance=72.9%
  - Abdominal pain=85.1%

CHS: Proposed Diagnostic Criteria
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3847982/

Essential for diagnosis
- Long-term cannabis use: More than 1 year, at least weekly

CHS: Proposed Diagnostic Criteria (continued)

Major features
- Severe cyclic nausea and vomiting
- Resolution with cannabis cessation
- Relief of symptoms with hot showers or baths
- Epigastric or periumbilical abdominal pain

Supportive features
- Age younger than 50 years
- Involuntary weight loss over 5 kg
- Morning predominance of symptoms
- Normal bowel habits
- Negative laboratory, radiographic and endoscopic test results
CHS – Pathogenesis

• Not well understood, proposed
  - Dose-dependent buildup of cannabinoids and related effects of cannabinoid toxicity
    • THC = Large volume of distribution, long T½
      - Likely genetic issue where cannabinoids not eliminated in typical manner

• Not well understood, proposed
  - Altered function of brain cannabinoid receptors including hypothalamus
    • Perhaps why reports of hot showers/bath relieve symptoms, possible thermoregulation dysfunction

CHS – Treatment

• Definitive
  - Discontinuation of cannabis use

• Supportive care
  - Intravenous fluids if needed
  - Dopamine antagonists such as metoclopramide (Reglan®)
  - Topical capsaicin cream

Topical Capsaicin for CHS Via Small Case Study Reports

• Mechanism of action
  - Not well understood
  - Possibly active at heat-activated receptors

• Dose
  - Capsaicin cream (0.0250–0.075%) to abdomen, limbs
  - Symptoms resolved/diminished within 30–45 minutes
    - Source: https://journals.lww.com/em-news/blog/BreakingNews/Pages/post.aspx?PostID=183

CHS Treatment

Yes or No

• Helpful or not?
  - 5-HT3 serotonin receptor antagonists No
    • Ondansetron (Zofran®)
    • Granisetron (Kytril®)
  - Phenothiazines No
    • Prochlorperazine (Compazine®)
    • Promethazine (Phenergan®)
  - Opioids (for pain management) No

A 28-year-old man presents with recently diagnosed CHS.

• He states, “I quit smoking weed a week ago and still get sick to my stomach.” You advise that in CHS, up to what period of cannabis abstinence is usually needed prior to full symptom resolution?
A 28-year-old man presents with recently diagnosed CHS.

A. 3–4 weeks  
B. 1–2 months  
C. 2–4 months  
D. 5+ months

32-year-old Woman with Chronic HCV

• Baseline hepatic enzymes  
  – AST=63 U/L  
  – ALT=212 U/L  

• After HD ibuprofen × 2 weeks for self treatment of minor ortho issue, develops RUQ abdominal pain  
  – AST=459 U/L  
  – ALT=1209 U/L

Potentially Hepatotoxic NSAID Effect in HCV

• NSAIDs  
  – AST and ALT in ~1–10%, particularly with HCV or other chronic liver disease  

• Etiology  
  – Immunogenic  
  – Metabolic idiosyncrasy  
  – Related to high renin state  

True or false?

Acetaminophen in standard doses can be used safely in patients with liver disease and is a preferred analgesic/antipyretic because of the absence of the platelet impairment, gastrointestinal toxicity, and nephrotoxicity associated with NSAIDs.

True


Information from an FDA Advisory: Phenytoin, Fosphenytoin Sodium, and Carbamazepine Associated with Potential Increased Risk of Serious Skin Reactions
Who is at risk for these reactions?

- According to FDA advisory
  - Note with phenytoin therapy in Asian patients positive for a particular human leukocyte antigen (HLA) allele, HLA-B*1502
  - HLA complex helps immune system distinguish the body’s own proteins from proteins made by foreign invaders including bacteria and viruses.

Who is at risk for these reactions? (continued)

- Presence of this genetic variation
  - Occurs almost exclusively in patients with ancestry across broad areas of Asia, including Han Chinese, Filipinos, Malaysians, South Asian Indians, and Thais, up to 10–15% of this population
  - Uncommon in other south Asians, Japanese, Koreans

What is the reaction?

- Toxic epidermal necrolysis (TEN)
  - Life-threatening skin disorder characterized by mucocutaneous reaction with widespread erythema, necrosis, epidermal and mucosal bullous detachment of the epidermis
  - End result = Skin exfoliation and resulting sepsis
  - With mucous membrane involvement, respiratory failure, GI bleed, ocular and GU complications

Clinical Images of Patients With Toxic Epidermal Necrolysis


Is this a disease state?

- Not abnormal or a marker of a disease state
  - Simply agenetic variation noted in aforementioned ethnic groups
  - No other known risk from having the allele
Other medication use implicated?

- Avoid use of the following in individual positive for this genetic variation
  - Fosphenytoin, prodrug converted to phenytoin after administration
  - Carbamazepine, as TEN noted in this risk group as well but continues to be investigated

Time frame for the reaction? Discontinue drug in at-risk individual?

- With carbamazepine use
  - >90% have this reaction within first few months of treatment
  - Long-term users who have not developed these problems considered low risk for future development of this reaction
- Similar observation with phenytoin use

Testing for the condition?

- HLA-B*1502 allele testing
  - Recommendations to test at-risk ethnic groups prior to initiating therapy with these medications

References

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