Spewing the facts: olanzapine for chemotherapy-induced nausea and vomiting (CINV)

Mark L. Zangardi, PharmD
PGY1 Pharmacy Practice Resident
Lahey Hospital & Medical Center
May 5, 2015
Disclosures

• No financial or personal disclosures

• Unlabeled use of medications will be referenced
Objectives

• Describe the evidence supporting the use of olanzapine for prevention and breakthrough treatment of CINV

• Identify clinical situations in which olanzapine may be utilized for CINV
Patient Case

• EM is a 38 year old female with newly diagnosed node-positive breast cancer (HER2/ER/PR negative)

• EM is starting adjuvant chemotherapy with dose-dense AC
  • Doxorubicin 60mg/m² + cyclophosphamide 600mg/m²

• You are tasked to design an antiemetic regimen
## Emetogenic potential

<table>
<thead>
<tr>
<th>Highly emetogenic (&gt;90%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisplatin</td>
</tr>
<tr>
<td>Cyclophosphamide (&gt; 1500 mg/m²)</td>
</tr>
<tr>
<td>Carmustine (&gt; 250 mg/m²)</td>
</tr>
<tr>
<td>Dacarbazine</td>
</tr>
<tr>
<td>Doxorubicin (≥ 60 mg/m²)</td>
</tr>
<tr>
<td><strong>Cyclophosphamide + doxorubicin/epirubicin</strong></td>
</tr>
</tbody>
</table>

Adapted from NCCN Antiemetic Guidelines 2.2014
Chemotherapy-induced nausea and vomiting (CINV)

• Acute: within 24 hours

• Delayed: after 24 hours

• Anticipatory: occurs prior to next chemotherapy administration

• Breakthrough: occurs despite prophylactic therapy
  • Requires “rescue” antiemetics
CINV background/epidemiology

- Among the most common and feared adverse effects in cancer patients\textsuperscript{1,2}

- Rates of nausea remain high despite the use of guideline-recommended prophylactic agents\textsuperscript{3,4}

## Risk factors

<table>
<thead>
<tr>
<th>Patient-related</th>
<th>Treatment-related</th>
</tr>
</thead>
<tbody>
<tr>
<td>Younger age</td>
<td>Chemotherapy emetogenicity</td>
</tr>
<tr>
<td>Female gender</td>
<td>Chemotherapy dose</td>
</tr>
<tr>
<td>Inexperience with alcohol</td>
<td>Prophylactic antiemetics</td>
</tr>
<tr>
<td>Emesis during pregnancy</td>
<td></td>
</tr>
<tr>
<td>Poor performance status</td>
<td></td>
</tr>
</tbody>
</table>

Neurotransmitters involved in emesis

- Serotonin
- Histamine
- GABA
- Dopamine
- Substance P
- Acetylcholine
- Endorphins

Adapted from Navari RM. *Eur J Pharmacol* 2014;722:180-6.
CINV prophylaxis for highly emetogenic chemotherapy (HEC)

- **5-HT$_3$ antagonist**
  - Dolasetron
  - Granisetron
  - Ondansetron
  - Palonosetron

- **Steroid**
  - Dexamethasone

- **NK-1 antagonist**
  - Aprepitant
  - Fosaprepitant

NCCN Antiemetic Guidelines 2.2014
Olanzapine

- Atypical antipsychotic medication

- Blocks multiple neurotransmitters
  - Dopamine: $D_1, D_2, D_3, D_4$
  - Serotonin: $5-HT_{2a}, 5-HT_{2c}, 5-HT_3, 5-HT_6$
  - Catecholamine: $\alpha_1$ adrenergic
  - Acetylcholine: muscarinic
  - Histamine: $H_1$

Olanzapine for prevention of CINV in HEC

Chemotherapy-naïve patients receiving HEC (n=241)

OPD intervention (n=121)
- Olanzapine 10mg PO daily on days 1-4
- Palonosetron 0.25mg IV on day 1
- Dexamethasone 20mg IV on day 1

APD intervention (n=120)
- Aprepitant 125mg PO on day 1, 80mg PO days 2-3
- Palonosetron 0.25mg IV on day 1
- Dexamethasone 12mg IV on day 1, 4mg PO BID days 2-4

Complete Response

Acute (0-24h) | Delayed (24-120h) | Overall (0-120h)

% of Patients

<table>
<thead>
<tr>
<th>OPD</th>
<th>APD</th>
</tr>
</thead>
<tbody>
<tr>
<td>97</td>
<td>87</td>
</tr>
<tr>
<td>77</td>
<td>73</td>
</tr>
<tr>
<td>77</td>
<td>73</td>
</tr>
</tbody>
</table>

P < 0.01

No Nausea

Acute (0-24h)

% of Patients

<table>
<thead>
<tr>
<th>OPD</th>
<th>APD</th>
</tr>
</thead>
<tbody>
<tr>
<td>87</td>
<td>87</td>
</tr>
</tbody>
</table>

Delayed (24-120h)
P < 0.01

Overall (0-120h)
P < 0.01

Olanzapine addition

Patients receiving MEC or HEC (n=44)

Dexamethasone
5-HT$_3$ antagonist
NK-1 antagonist

Olanzapine 5mg PO daily on days 0-5 (n=22)

Placebo PO on days 0-5 (n=22)

Olanzapine addition

86

55

64

23

59

23

Acute phase (P = 0.045)  Delayed phase (P = 0.014)  Overall phase (P = 0.031)

% of patients achieving total control*

*Total control = no vomiting, no use of rescue medication, maximum nausea of <5/100 mm on visual analog scale

Olanzapine for breakthrough CINV

Day 1: DEX 12mg IV, PAL 0.25mg IV, FOS 150mg IV

Days 2-4: DEX 4mg PO BID (n=276)

No CINV (n=164)
Lost (n=1)
Discontinued (n=3)

Olanzapine 10mg PO q24h for 72 hours (n=56)

Metoclopramide 10mg PO q8h for 72 hours (n=52)

DEX = dexamethasone; PAL = palonosetron; FOS = fosaprepitant

Olanzapine for breakthrough CINV

- No emesis (P < 0.01): 70% for Olanzapine vs. 31% for Metoclopramide
- No nausea (P < 0.01): 68% for Olanzapine vs. 23% for Metoclopramide

CINV prophylaxis for highly emetogenic chemotherapy (HEC)

Conventional regimen

5-HT₃ antagonist
Dolasetron
Granisetron
Ondansetron
Palonosetron

Steroid
Dexamethasone

NK-1 antagonist
Aprepitant
Fosaprepitant

Alternative regimen

5-HT₃ antagonist
Palonosetron

Steroid
Dexamethasone

Atypical antipsychotic
Olanzapine

NCCN Antiemetic Guidelines 2.2014
## Cost Considerations

<table>
<thead>
<tr>
<th></th>
<th>Aprepitant</th>
<th>Fosaprepitant</th>
<th>Olanzapine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Price</strong></td>
<td><strong>$594.06</strong></td>
<td><strong>$308.35</strong></td>
<td><strong>$47.96</strong></td>
</tr>
<tr>
<td><strong>Dosage</strong></td>
<td>One 125mg tablet</td>
<td>One 150mg vial</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Two 80mg tablets</td>
<td></td>
<td>Four 10mg tabs</td>
</tr>
</tbody>
</table>

*Calculated from average wholesale price (AWP)*
Summary

- Olanzapine is an effective antiemetic
  - Prevention of CINV (particularly delayed-phase)
  - Treatment of breakthrough CINV

- Olanzapine may provide significant cost-savings when compared to aprepitant
Acknowledgements

• Elizabeth O’Gara, PharmD, BCPS

• Brigitte Gil, PharmD, BCPS, BCOP
References


Drug Interactions Between Inhaled/Nasal or Intra-Articular Corticosteroids and Antiretrovirals (ARV)

Jillian Stanton, PharmD.
PGY1 Pharmacy Practice Resident
Virginia Commonwealth University Health System
Learning Objectives

- Identify patients at risk for a clinically significant drug-drug interaction between ritonavir- or cobicistat-boosted ARV regimens and inhaled/nasal or intra-articular corticosteroids.

- Prepare a treatment recommendation for HIV-positive patients requiring ARV therapy and non-oral corticosteroids.
Patient Case: TC

- Reason for visit: 67 y/o WM with HIV presenting for routine follow up appointment.

- Interval History:
  - HIV diagnosis: 2010
  - Started on antiretrovirals in October 2013
  - Hospitalized April 27th-30th 2014 for a significant asthma attack
Patient Case: TC

- Home Medications:
  - Atazanavir 300mg PO daily
  - Ritonavir 100mg PO daily
  - Emtricitabine-tenofovir (200mg/300mg) PO daily
  - Fluticasone-salmeterol (200mcg/50mcg) inhalation BID (*Started during hospitalization*)
  - Insulin glargine 10U subcutaneous injection at bedtime (*started during hospitalization*)
Patient Case: TC

Which drug combination is contributing to TC’s elevated blood sugars?

A. Ritonavir and atazanavir
B. Fluticasone-salmeterol and ritonavir
C. Fluticasone-salmeterol and emtricitabine-tenofovir
D. Fluticasone-salmeterol and atazanavir
Inhaled/Nasal Corticosteroids and ARVs

- Ritonavir and Cobicistat:
  - *Strong CYP3A4 inhibitors*
- Inhaled/nasal Corticosteroids:
  - *CYP3A4 substrates*
- Concurrent Administration:
  - ↑ systemic cortisol concentrations
- Consequences:
  - Cushing’s syndrome subsequent adrenal suppression
  - Hyperglycemia
  - Osteoporosis

Signs and Symptoms of Cushing’s

- Abnormal fat distribution:
  - Buffalo neck
  - Moon facies
  - Facial atrophy

- Increased body weight

- Proximal myopathy

- Cutaneous changes:
  - Abdominal stretch
  - Fragility, ecchymosis, purpura

- Hyperandrogenism:
  - Hirsutism, acne
  - Oligomenorrhea, amenorrhea

- Hypertension

- Emotional changes

- Impaired glucose tolerance

- Osteoporosis

## Clinical Evidence

<table>
<thead>
<tr>
<th>Gender</th>
<th>Age</th>
<th>Inhaled Corticosteroid*</th>
<th>Protease Inhibitor</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>9</td>
<td>Fluticasone (I)</td>
<td>Ritonavir, lopinavir</td>
<td>Cushing’s syndrome</td>
</tr>
<tr>
<td>Female</td>
<td>10</td>
<td>Fluticasone (I)</td>
<td>Ritonavir, lopinavir</td>
<td>Cushing’s syndrome</td>
</tr>
<tr>
<td>Male</td>
<td>16</td>
<td>Fluticasone (I)</td>
<td>Ritonavir, fosamprenavir</td>
<td>Cushing’s syndrome</td>
</tr>
<tr>
<td>Female</td>
<td>31</td>
<td>Fluticasone (I)</td>
<td>Ritonavir, lopinavir</td>
<td>Cushing’s syndrome</td>
</tr>
<tr>
<td>Male</td>
<td>42</td>
<td>Fluticasone (I)</td>
<td>Ritonavir, lopinavir</td>
<td>Cushing’s syndrome</td>
</tr>
</tbody>
</table>

*Inhaled= I  
*Nasal= N

## Clinical Evidence

<table>
<thead>
<tr>
<th>Gender</th>
<th>Age</th>
<th>Nasal Corticosteroid</th>
<th>Protease Inhibitor</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>4</td>
<td>Budesonide (N)</td>
<td>Lopinavir/Ritonavir</td>
<td>Adrenal insufficiency</td>
</tr>
<tr>
<td>Male</td>
<td>9</td>
<td>Fluticasone (N)</td>
<td>Lopinavir/Ritonavir</td>
<td>Adrenal insufficiency</td>
</tr>
<tr>
<td>Male</td>
<td>60</td>
<td>Fluticasone (N)</td>
<td>Atazanavir/Ritonavir</td>
<td>Adrenal insufficiency</td>
</tr>
</tbody>
</table>

*Inhaled= I
*Nasal= N

Management

- Discontinue to inhaled/nasal corticosteroid
- Follow patient closely adrenal insufficiency
- Consider lower risk corticosteroids

<table>
<thead>
<tr>
<th>Inhaled Corticosteroid</th>
<th>Metabolism</th>
<th>Receptor Binding Affinity (Dexamethasone= 100)</th>
<th>Protein Binding (%)</th>
<th>Lipophilicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beclomethasone dipropionate</td>
<td>Esterase and CYP3A4</td>
<td>43</td>
<td>87</td>
<td>1.3</td>
</tr>
<tr>
<td>Budesonide</td>
<td>CYP3A4</td>
<td>855</td>
<td>85-90</td>
<td>1.9</td>
</tr>
<tr>
<td>Fluticasone propionate</td>
<td>CYP3A4</td>
<td>1910</td>
<td>99</td>
<td>3.4</td>
</tr>
<tr>
<td>Fluticasone furoate</td>
<td>CYP3A4</td>
<td>2990</td>
<td>99</td>
<td>No Data</td>
</tr>
<tr>
<td>Flunisolide</td>
<td>Glucoronidation sulfation</td>
<td>180</td>
<td>80</td>
<td>1.1</td>
</tr>
<tr>
<td>Mometasone furoate</td>
<td>CYP3A4</td>
<td>2200</td>
<td>98.5</td>
<td>3.4</td>
</tr>
</tbody>
</table>
Management

- Discontinue to inhaled/nasal corticosteroid
- Follow patient closely adrenal insufficiency
- Consider lower risk corticosteroids

<table>
<thead>
<tr>
<th>Inhaled Corticosteroid</th>
<th>Metabolism</th>
<th>Receptor Binding Affinity (Dexamethasone= 100)</th>
<th>Protein Binding (%)</th>
<th>Lipophilicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beclomethasone diproprionate</td>
<td>Esterase and CYP3A4</td>
<td>43</td>
<td>87</td>
<td>1.3</td>
</tr>
<tr>
<td>Budesonide</td>
<td>CYP3A4</td>
<td>855</td>
<td>85-90</td>
<td>1.9</td>
</tr>
<tr>
<td>Fluticasone propionate</td>
<td>CYP3A4</td>
<td>1910</td>
<td>99</td>
<td>3.4</td>
</tr>
<tr>
<td>Fluticasone furoate</td>
<td>CYP3A4</td>
<td>2990</td>
<td>99</td>
<td>No Data</td>
</tr>
<tr>
<td>Flunisolide</td>
<td>Glucoronidation sulfation</td>
<td>180</td>
<td>80</td>
<td>1.1</td>
</tr>
<tr>
<td>Mometasone furoate</td>
<td>CYP3A4</td>
<td>2200</td>
<td>98.5</td>
<td>3.4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Design</strong></th>
<th>Open label, prospective, randomized PK/PD study</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Population</strong></td>
<td>30 healthy volunteers aged 18-60 with no underlying medical conditions</td>
</tr>
</tbody>
</table>
| **Intervention**    | Volunteers all received beclomethasone dipropionate (BDP) for 14 days and were randomized into 3 groups:  
• Control:  BDP alone for 28 days  
• BDP + ritonavir 100mg BID for 28 days  
• BDP + darunavir/ritonavir (600/100) BID for 28 days |
| **Primary Outcome** | Geometric mean ratios (day 28: day 14) |
| **Results**         | Control: 0.93 (0.81-1.06, p=0.61)  
BDP + ritonavir : 2.08 (1.52-2.65, p=0.006)  
BDP + darunavir/ritonavir: 0.89 (0.68-1.09, p=0.61) |
|                     | There were no significant differences in serum cortisol levels |
| **Conclusions**     | Darunavir/ritonavir did not increase exposure to BDP exposure |
Patient Case: MN

- Reason for Visit: 60 y/o AAF with multidrug resistant HIV and osteoarthritis (OA) presenting for assistance in ART adherence

- Current ART regimen:
  - Darunavir/cobicistat 800mg/150mg PO once daily
  - Dolutegravir 50mg PO twice daily
  - Tenofovir 300mg PO daily
Patient Case: MN

- Patient reveals that she has been getting corticosteroid injections for treatment of OA. Her last shot injection was 4/8/2014.

- How would you respond?
  A. Since corticosteroid injections are localized, there is no risk of corticosteroid toxicity
  B. Cobicistat does not have the same risks as ritonavir, there is no risk of corticosteroid toxicity
  C. Switch patient to a nonnucleoside reverse transcriptase inhibitor regimen
  D. Continue current ART regimen and monitor closely
Clinical Evidence: Intra-articular Corticosteroids

- Case #1:
  - 47 y/o male
  - On atazanavir/ritonavir
  - Received trimacinolone injections (blood conc.= 0.52)
  - Developed hypercortisolism
  - Return to baseline: 3 months

- Case #2:
  - 47 y/o female
  - On abacavir/ritonavir
  - Received triamcinolone injections (blood conc.=1.1)
  - Developed hypercortisolism
  - Return to baseline: 10 weeks

Management

- Consider switching patient to a PI- or cobicistat-sparing regimen
- Carefully monitor for signs and symptoms of Cushing’s syndrome
  - A morning cortisol and ACTH concentration to assess for adrenal suppression (*may last 2 or more weeks*)
- Physiologic doses of glucocorticoid replacement with hydrocortisone may be necessary
- *Education and prevention is key*

Patient Case: MN

- Patient reveals that she has been getting corticosteroid injections for treatment of OA. Her last shot injection was 4/8/2014.

- How would you respond?
  - A. Since corticosteroid injections are localized, there is no risk of corticosteroid toxicity
  - B. Cobicistat does not have the same risks as ritonavir, there is no risk of corticosteroid toxicity
  - C. Switch patient to a nonnucleoside reverse transcriptase inhibitor regimen
  - D. Continue current ART regimen and monitor closely
References


The use of loratadine for the treatment of bone pain in cancer patients

Eastern States Conference 2015

Kathryn Yee, PharmD
Johns Hopkins Bayview Medical Center, PGY1 Pharmacy Resident

May 11, 2015
Disclosure

• I have no actual or potential conflict of interests in relation to this program
Objectives

• To discuss treatment options for bone pain in cancer patients
• To evaluate the mechanism of action of loratadine in treating bone pain in cancer patients that are refractory to non-steroidal anti-inflammatory drugs (NSAIDs) and opioids
Patient case

• KJ is a 49 year old female recently diagnosed with acute promyelocytic leukemia (APL)
• Started on all trans-retinoic acid (ATRA) and arsenic for treatment of APL
Patient KJ

- CC: Day 6 of treatment KJ complains of pain
  - Pain in knees, hips, shins, and ribs
  - Dull, constant, and migrates
  - Varies from 5-10/10 throughout the day
Bone pain in cancer patients

- **Etiology:**
  - Metastases to the bones
  - Result of disease
  - Side effect of biologic modifiers

- **Pathophysiology:**
  - Changes in bone marrow pressure and inflammation
  - Inflammatory and neuropathic pain

S. Falk and A. JCO. 2014. 32(16):1647-1654
M. Aisner and T. Hoxie. NEJM. 1948. 238(21): 733-737
Signs and symptoms

• Pain and tenderness along the bones and the joints
  – More noticeable in the larger bones
  – Bone marrow stimulation greatest in the pelvis and femur
• Multiple, migratory joint pain
• Fatigue
• Not identifiable on X-rays
Goals of therapy

• Relieve pain
• Prevent risk of fractures
• Prevent or delay bone complications

S. Falk and A. JCO. 2014. 32(16):1647-1654
Clinical impact of bone pain

- Increase risk for falls and fractures
- If related to granulocyte stimulating growth factors:
  - Discontinuation of growth factors
  - May require a decrease in chemotherapy dose intensity
  - Possibility of decreasing response outcomes
- Decrease in quality of life
  - Pain is “worse than receiving chemotherapy” and with little relief with common pain medications

C. Romeo et al. J Oncol Pharm Pract. 2014; 0(0)1-4
Current treatment options

- Opioids
- Nonsteroidal anti-inflammatory drugs (NSAIDs)
- Acetaminophen
- Steroids
- Bisphosphonates
Patient KJ

- **Pain regimen:**
  - Oxycodone 5 mg PO q4h prn
  - Switched to morphine 2 mg IV q3h prn
  - Switched to hydromorphone 0.5 mg IV q4h prn

- **NSAIDS**
  - Platelet count 74

- **Differentiation syndrome and leukocytosis**
  - Dexamethasone 10mg IV q12h
Loratadine

- **Class:** tricyclic antihistamine, second generation
- **Indications:** allergic rhinitis and urticaria
- **Dosage:** 10 mg once daily
- **Mechanism of action:**
  - Selective histamine-1 receptor antagonist
  - May have some anti-inflammatory properties

A. Guinigundo, et al. NCT 01712009
L. Kennedy, et al. NCT02305979
C. Romeo et al. J Oncol Pharm Pract. 2014; 0(0):1-4
Loratadine and bone pain

- Stimulation of the bone marrow may cause inflammation
- Bone marrow edema may cause release of histamine
- Anti-histamine may decrease pain by decreasing bone edema

A. Guinigundo, et al. NCT01712009
L. Kennedy, et al. NCT02305979
C. Romeo et al. J Oncol Pharm Pract. 2014; 0(0)1-4
Patient KJ

- Bone pain etiology:
  - Side effect of ATRA therapy
  - Leukemia

- Pain relief:
  - No relief with opioids
  - Received loratadine for two days
  - Pain did dissipate with continuation of therapy for APL
Clinical Trials

- Ongoing phase II trials evaluating the efficacy of loratadine to reduce granulocyte stimulating factor induced bone pain
  - Loratadine for the prevention of bone pain
    - Cancer and Leukemia Group B (CALBG) (NCT01311336)
    - NOLAN: Naproxen or Loratadine and Neulasta (NCT01712009)
- Loratadine in patients with hematologic malignancies (NCT02305979)
Which of the following are used for bone pain?

A. Hydromorphone
B. Ibuprofen
C. Prednisone
D. Zoledronic acid
E. All of the above
How does loratadine decrease pain?

A. Decreases inflammation by increasing the release of inflammatory factors

B. Has been shown to have analgesia properties

C. Blocking histamine receptors to reduce bone marrow edema

D. The mechanism is unknown
Conclusion

• Loratadine may be a potential alternative to bone pain refractory to other treatment options
• Etiology of bone pain may impact the efficacy of loratadine
• Randomized trials are currently being conducted to assess the efficacy of loratadine in bone pain related to G-CSF
References

• A. Bennett. The role of biochemical mediators in peripheral nociception and bone pain. Cancer Surv. 1988; 7:55-67
• A. Guinigundo, et al. prophylactic naproxen or loratadine for bone pain in patients with breast cancer receiving chemotherapy and pegfilgrastim: a randomized, phase II study (NOLAN) AMGEN 20110147; NCT 01712009
• L. Kennedy, et al. Evaluation of loratadine for G-CSF induced bone pain in patients with hematologic malignancies. NCT02305979
• C. Romeo et al. Severe pegfilgrastim-induced bone pain completely alleviated with loratadine: a case report. J Oncol Pharm Pract. 2014; 0(0)1-4
• M. Lambertini, et al. The five “Ws” for bone pain due to the administration of granulocyte-colony stimulating factors (G-CSFs). Crit Rev Onc/Heme. 2014; 89:112-128
The use of loratadine for the treatment of bone pain in cancer patients

Eastern States Conference 2015

Kathryn Yee, PharmD
Johns Hopkins Bayview Medical Center, PGY1 Pharmacy Resident
Disclosures

There is no commercial support associated with this educational activity. Each presenter and planning committee member has disclosed no relationship with any commercial company. There will be no presentation of off-label use of any drug or medical device.
Objectives

• Identify two differences between current and new labeling regulations

• List three main sections of the new pregnancy and lactation labeling
BACKGROUND
Current labeling

8.1 Pregnancy
• Pregnancy category (A, B, C, D, X)
• Risk summary
• Data

8.2 Labor and Delivery
• Risk summary
• Data

8.3 Nursing mothers
• Risk summary
• Data
Timeline for labeling changes

Prior to 6/30/01

6/30/01 - 6/29/02

6/30/02 - 6/29/05

6/30/05 – 6/30/07

6/30/07 – 6/30/15

Labeling effective 6/30/2015 (NDA vs pending applications)

Why is there new labeling?

• To provide information in a conducive format for patient counseling and to relay clinical information effectively

• Assist health care providers in assessing benefit versus risks

• Allow for informed decisions

NEW LABELING
New labeling

- Fetal and pregnancy risk summary
- Clinical considerations (new)
- Supporting data
- Removal of pregnancy categories
- Requires most updated information

### 8.1 Pregnancy Labeling

<table>
<thead>
<tr>
<th>Section information</th>
<th>Risk summary</th>
<th>Clinical Considerations</th>
<th>Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Required?</td>
<td>Omit if not applicable</td>
<td>Required subheading</td>
<td>Omit if none of the headings are applicable</td>
</tr>
</tbody>
</table>

#### Section information
- Common statement
- Contact information for registry
- Risk of adverse developmental outcomes
- Disease associated maternal and/or embryo/fetal risk
- Dose adjustment during pregnancy and postpartum period
- Maternal adverse reactions
- Fetal/neonatal adverse reactions
- Labor or delivery
- Human data
- Animal data
## 8.2 Lactation Labeling

<table>
<thead>
<tr>
<th>Section</th>
<th>Risk summary</th>
<th>Clinical Considerations</th>
<th>Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Required?</td>
<td>Required subheading</td>
<td>Omit if not applicable</td>
<td>Omit if not applicable</td>
</tr>
<tr>
<td>Section information</td>
<td>• Presence of a drug and/or its active metabolite(s) in human milk</td>
<td>• Minimizing exposure</td>
<td>• Human data</td>
</tr>
<tr>
<td></td>
<td>• Effects of a drug and/or its active metabolite(s) on the breastfed child</td>
<td>• Monitoring for adverse reactions</td>
<td>• Animal data</td>
</tr>
<tr>
<td></td>
<td>• Effects of a drug and/or its active metabolite(s) on milk production</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

# 8.3 Females & Males of Reproductive Potential

<table>
<thead>
<tr>
<th>Headings</th>
<th>Main section</th>
</tr>
</thead>
<tbody>
<tr>
<td>Required?</td>
<td>Omit if none of the subheadings are applicable</td>
</tr>
</tbody>
</table>
| Section information       | • Recommendations for pregnancy testing and contraception  
                              • Drug-associated effects on fertility (human or animal data)  
                              • Pregnancy testing  
                              • Contraception  
                              • Infertility                                                   |

Drafts and Publications

• Rule to be published in Federal Register

• FDA currently accepting draft comments for Industry guidance on the rule
SUMMARY
## Similarities and Differences

<table>
<thead>
<tr>
<th>Similarities</th>
<th>Differences</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Goal</td>
<td>• Clinical considerations</td>
</tr>
<tr>
<td>• Risk summary</td>
<td>• Removal of categories</td>
</tr>
<tr>
<td>• Data</td>
<td>• New section 8.3</td>
</tr>
<tr>
<td></td>
<td>• Conducive format</td>
</tr>
</tbody>
</table>
Significance for pharmacists

- Pregnancy rate for U.S. women in 2009 was 102.1 per 1,000 women aged 15–44.

- Most women (about 90%) take at least one medication during pregnancy and 70% take at least one prescription medication.

---


Significance for pharmacists

• Pharmacists routinely provide medications and counseling to patients

• New labeling will positively affect pharmacy practice, by having relevant information in one place and making counseling more individualized
LEARNING ASSESSMENT
Question #1

• What are two differences between the old and new labeling?
  a) Risk summary
  b) Clinical considerations
  c) Data
  d) Removal of pregnancy categories
  e) a & c
  f) b & d
  g) None of the above
Question #1

- What are two differences between the old and new labeling?
  a) Risk summary
  b) Clinical considerations
  c) Data
  d) Removal of pregnancy categories
  e) a & c
  f) b & d
  g) None of the above
Question #2

• What are the sections in the new labeling?
  a) 8.1 Pregnancy including labor and delivery
  b) 8.2 Lactation including nursing mothers
  c) 8.3 Females and males of reproductive potential
  d) All of the above
Question #2

• What are the sections in the new labeling?
  a) 8.1 Pregnancy including labor and delivery
  b) 8.2 Lactation including nursing mothers
  c) 8.3 Females and males of reproductive potential
  d) All of the above
Conclusion

- Changes to labeling
- Significance for pharmacy
- Conducive format & removal of categories
- Individualized counseling

PLLR
References


Questions?
Eastern States Residency Conference

Pregnancy and Lactation Labeling Rule

Indrani Kar, PharmD
Drug Information Resident
Robert Wood Johnson University Hospital
May 2015
Enterococcal Infective Endocarditis: Reconsidering Aminoglycosides

Denise Dong, Pharm.D.
PGY-1 Pharmacy Practice Resident
SUNY Downstate Medical Center
Conflict of Interest Statement

No conflict of interest to disclose
Objectives

- Identify patients that are potential candidates for beta-lactam combination therapy

- Develop an individualized antibiotic regimen for patient with *Enterococcus faecalis* infective endocarditis with a high level of aminoglycoside resistance
Infective Endocarditis (IE)

- Infection of the endocardium

- Most common organisms
  - Staphylococci species (42%)
  - Streptococci species (29%)
  - Enterococci species (~10%)
    - *E. faecalis* (~90%)
    - *E. faecium*
Challenges of Enterococcal Infections in IE

- Limited selection of antibiotic therapy with bactericidal activity
- Decreased susceptibility to penicillin and ampicillin
- Intrinsic resistance to most cephalosporins
- Intrinsic resistance to aminoglycosides
- Ability to acquire resistance to currently available antibiotics

2005 American Heart Association Recommendations

- Treatment of enterococcal IE
  - Combination of cell wall-active agent + aminoglycoside for duration of 4-6 weeks
    - Cell wall-active agent: penicillin, ampicillin, or vancomycin
    - Aminoglycosides: gentamicin or streptomycin

- Antibiotic synergy
  - Cell wall-active agent inhibits bacterial growth and increases permeability of aminoglycosides to induce bactericidal effect

Development of Resistance

- **Enterococcus faecium**
  - More intrinsically resistant to B-lactam antibiotics
  - Glycopeptide resistance
  - Intrinsic aminoglycoside resistance (amikacin and tobramycin)

- **Enterococcus faecalis**
  - B-lactam resistance rare
  - Aminoglycoside resistance
    - Intrinsic aminoglycoside resistance
    - Acquire resistance: high-level resistance to aminoglycosides (HLRA)

Aminoglycoside Resistance

- **Gentamicin**
  - Clinical limit for in vivo benefit: MIC > 500 mcg/ml
  - Mechanism of resistance
    - Acquisition of mobile genetic material

- **Streptomycin**
  - Clinical limit for in vivo benefit: MIC > 2000 mcg/ml
  - Mechanism of resistance
    - Reduction of binding affinity secondary to ribosomal point mutation of 30S subunit

Alternative Treatment

- Double beta-lactam therapy regimen
  - Ampicillin 2g every 4 hours and ceftriaxone 2g every 12 hours for duration of 6 weeks

- Proposed mechanism of action
  - Complete saturation of PBP 2 and PBP 3 by 3rd generation cephalosporin decreases MIC for amino-penicillin at PBP 4 and PBP 5

Mechanism of Action

Complete saturation by 3rd generation cephalosporins partially disrupt peptidoglycan synthesis.

Additional binding of PBP by amino-penicillin result in cell lysis.
Patient Selection

- Presence of HLRA
- High risk of renal failure
- Aminoglycoside-associated toxicity
- Blood culture with susceptibility to ampicillin
- Relapse after treatment with 1st line regimen

Candidate for DBLT

Review Questions

1. Which of the following patients diagnosed with enterococcal IE would benefit most from DBLT?

   a. 68 YOM presents with AKI and culture isolated non-HLRA *E. faecalis* and susceptible to ampicillin
   b. 62 YOF with positive blood culture for non-HLRA *E. faecalis* with resistance to ampicillin
   c. 58 YOF with positive blood culture for *E. faecium* with resistance to vancomycin
   d. 65 YOM with positive blood culture for *E. faecalis* with acquired resistance to ampicillin and high-level resistance to gentamicin
Limitations of DBLT

- Prolonged exposure to 3rd generation cephalosporins increases risk of developing:
  - Vancomycin resistance enterococci (VRE)
  - Clostridium difficile

- Limited experience compared with 1st line therapy

- Lack of randomized control trials

Conclusion

- Increasing incidence of HLRA in *E. faecalis* infections
- Double beta-lactam therapy is an alternative therapy regimen for *E. faecalis* IE
- Treatment should be individualized to patient’s susceptibility and risk factors for resistance
2. AF is a 67 YOF with persistent bacteremia and confirmed diagnosis of IE. Her blood culture is positive for *E. faecalis* with resistance to gentamicin (MIC > 500 mcg/ml) and streptomycin (MIC > 2000 mcg/ml) synergy. What is your recommendation to the team?

a. Ampicillin and gentamicin
b. Penicillin and streptomycin
c. Ampicillin and ceftriaxone
d. Vancomycin and ceftriaxone
Review Questions

3. What is the synergistic mechanism of double beta-lactam therapy (DBLT)?

a. Cell wall-active agent increases permeability of aminoglycoside to inhibit 30S ribosomal subunit
b. Saturation of PBPs 2 and 3 by a 3rd generation cephalosporin reduces MIC of amino-penicillin
c. Cell wall-active agent increases permeability of quinolones to inhibit topoisomerase II activity
d. Saturation of PBPs 4 and 5 by amino-penicillin reduce MIC of 3rd generation cephalosporins
4. Which of the following are potential limitations of DBLT?
   
   I. Nephrotoxicity  
   II. Acquiring resistance to vancomycin  
   III. Development of C. difficile

   a. I only  
   b. I and II  
   c. II and III  
   d. I, II, and III
Reference


Questions?
Weight-based Enoxaparin for Venous Thromboembolism (VTE) Prophylaxis in Surgical/Trauma Patients

Jackie Finger, PharmD
PGY-1 Pharmacy Practice Resident
May 5, 2015
Disclosure

- I have no conflicts of interest to disclose.
Objectives

- Recognize pitfalls in using standard fixed dosing of enoxaparin for VTE prophylaxis
- Identify critically ill patients who may benefit from weight-based dosing of enoxaparin
Patient Case

BC is a 42 YOM brought to the STICU after undergoing surgery for bilateral femur fractures following a high-speed MVC. He is not actively bleeding and his Hgb is stable. What DVT prophylaxis would you recommend?

Weight: 120 kg       SCr: 1.3 mg/dL

A. UFH 5000 units SC every 8 hours
B. Enoxaparin 30 mg SC every 12 hours
C. Enoxaparin 40 mg SC daily
D. Enoxaparin 60 mg SC every 12 hours
## VTE Risk in Trauma

### Risk Factors and Odds Ratios

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>“Screening” Center</td>
<td>2.16</td>
</tr>
<tr>
<td>Age ≥40</td>
<td>2.00</td>
</tr>
<tr>
<td>Major Surgery</td>
<td>4.79</td>
</tr>
<tr>
<td>Ventilator days ≥3</td>
<td>5.14</td>
</tr>
<tr>
<td>Extremity injury</td>
<td>1.96</td>
</tr>
<tr>
<td>Head injury</td>
<td>1.53</td>
</tr>
</tbody>
</table>

*Chest 2012;141(2_suppl): e227S-e277S.*

VTE Risk in Trauma

- 0.76% DVT rate in trauma patients
- 2.8% DVT rate in trauma ICU patients at VCUHS
- 60-80% reduction in risk with LMWH

Chest 2012;141(2_suppl):e227S-e277S.
**Enoxaparin Pharmacokinetics**

- **Absorption**: linear, F= 91-100%, peak 3-5 hrs
- **Distribution**: 4.3 L
- **Metabolism**: hepatic
- **Excretion**: urine, $t_{1/2} = 4.5-7$ hrs, CL=0.83-1.86 L/h
- **Populations with altered PK**: pregnancy, obese, renal impairment


*Lovenox (enoxaparin) package insert, 2013.*
Enoxaparin PK/PD (Haas et al.)
<table>
<thead>
<tr>
<th>Previous Literature</th>
<th>Malinoski 2010</th>
<th>Costantini 2013</th>
<th>Bickford 2013</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Prospective observational study, trauma/surgical ICU pts</td>
<td>- Enoxaparin 30 mg Q12h, n=54</td>
<td>- Enoxaparin 30 mg Q12h, n=61</td>
<td>- Prospective, obese trauma pts</td>
</tr>
<tr>
<td>- Anti-Xa trough low in 50% of pts</td>
<td></td>
<td>- Lower peaks: male, ↑ weight, ↑ BSA, ↑ body mass</td>
<td>- Enoxaparin 0.5 mg/kg Q12h, Adjust dose by 20 mg/day based on anti-Xa, n=86</td>
</tr>
<tr>
<td>- Low trough → low peak</td>
<td></td>
<td>- Trough did not correlate with peak</td>
<td>- Mean age 52 yrs, median wt 113.3 kg, median BMI 35.3 kg/m²</td>
</tr>
<tr>
<td></td>
<td>- VTE 14/54 (26%), 1 PE</td>
<td>- 43/61 (70.5%) had low peak</td>
<td>- Goal anti-Xa: 74/86 (86%)</td>
</tr>
<tr>
<td></td>
<td>- Anti-Xa trough low in 50% of pts</td>
<td></td>
<td>- Mean anti-Xa: 0.42 ± 0.1 IU/mL</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- DVT: 18/86 (21%)*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- No difference in anti-Xa in DVT pts</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- No bleeding</td>
</tr>
</tbody>
</table>
### Malinoski 2010
- **Prospective observational study, trauma/surgical ICU pts.**
- Enoxaparin 30 mg Q12h
- n=54
- VTE 14/54 (26%), 1 PE
- Anti-Xa trough low in 50% of pts.

### Costantini 2013
- **Prospective, open-label cohort, trauma pts.**
- Enoxaparin 30 mg Q12h
- n=61
- 43/61 (70.5%) had low peak
- Male, weight, body mass, BSA=lower peak
- Trough did not correlate with peak

### Bickford 2013
- **Prospective, obese trauma pts.**
- Enoxaparin 0.5 mg/g Q12h
- Adjust dose by 20 mg/day based on anti-Xa
- n=86
- Mean age 52 yrs., median wt. 113.3 kg, median BMI 35.3 kg/m²
- Goal anti-Xa: 74/86 (86%)
- Mean anti-Xa: 0.42 ± 0.1 IU/mL
- DVT: 18/86 (21%)*
- No difference in anti-Xa in DVT pts.
- No bleeding
VCUHS Protocol

Surgical Critical Care

Enoxaparin
0.5 mg/kg/dose
every 12 hours

Round dose to nearest 10 mg
No dose capping

Exclusions:
-CrCl<30 mL/min
-epidural catheter
-TBI + intracranial bleed
-HIT
-active hemorrhage
VCUHS Protocol

Peak anti-Xa level

- anti-Xa < 0.2 IU/mL: Increase dose by 20 mg/day
- anti-Xa > 0.6 IU/mL: Decrease dose by 20 mg/day

*CHEST reference range: 0.2-0.6 IU/mL

Chest 2012; 141(2_suppl):e691S-e736S.
## Results

- **n=19**

<table>
<thead>
<tr>
<th>Baseline Data</th>
<th>Mean</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>54.1 ± 16.4</td>
<td>21-86</td>
</tr>
<tr>
<td>Wt (kg)</td>
<td>112.8 ± 37.2</td>
<td>66.3-208</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>39.7 ± 13.8</td>
<td>22-66</td>
</tr>
<tr>
<td>SCr (mg/dL)</td>
<td>0.79 ± 0.3</td>
<td>0.36-1.50</td>
</tr>
</tbody>
</table>
## Results

- n=19

<table>
<thead>
<tr>
<th>anti-Xa (IU/mL)</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.2</td>
<td>4 (21.1)</td>
</tr>
<tr>
<td>0.2-0.29</td>
<td>7 (36.8)</td>
</tr>
<tr>
<td>0.3-0.39</td>
<td>5 (26.3)</td>
</tr>
<tr>
<td>0.4-0.49</td>
<td>1 (5.3)</td>
</tr>
<tr>
<td>0.5-0.59</td>
<td>2 (10.5)</td>
</tr>
<tr>
<td>&gt;0.6</td>
<td>0</td>
</tr>
</tbody>
</table>
## Results

- n=19

<table>
<thead>
<tr>
<th>anti-Xa (IU/mL)</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.2</td>
<td>4 (21.1)</td>
</tr>
<tr>
<td>0.2-0.29</td>
<td>7 (36.8)</td>
</tr>
<tr>
<td>0.3-0.39</td>
<td>5 (26.3)</td>
</tr>
<tr>
<td>0.4-0.49</td>
<td>1 (5.3)</td>
</tr>
<tr>
<td>0.5-0.59</td>
<td>2 (10.5)</td>
</tr>
<tr>
<td>&gt;0.6</td>
<td>0</td>
</tr>
</tbody>
</table>
Results

![Graph showing the relationship between weight (kg) and anti-Xa (IU/mL). The graph plots weight on the x-axis and anti-Xa on the y-axis, with data points scattered across the graph.](image)
Results

SCr (mg/dL)

anti-Xa (IU/mL)
Limitations

- Retrospective design, not controlled
Limitations

- Retrospective design, not controlled
- Did not assess non-pharmacologic prophylaxis
Limitations

- Retrospective design, not controlled
- Did not assess non-pharmacologic prophylaxis
- Anti-Xa levels drawn Monday-Friday
Discussion

- Correlation of anti-Xa and VTE rates?
- Duplex: the more you look, the more you find?
Patient Case

BC is a 42 YOM brought to the STICU after undergoing surgery for bilateral femur fractures following a high-speed MVC. He is not actively bleeding and his Hgb is stable. What DVT prophylaxis would you recommend?

Weight: 120 kg  SCr: 1.3 mg/dL

A. UFH 5000 units SC every 8 hours
B. Enoxaparin 30 mg SC every 12 hours
C. Enoxaparin 40 mg SC daily
D. Enoxaparin 60 mg SC every 12 hours
Standard fixed dosing of enoxaparin in critically ill surgical/trauma patients often results in sub-therapeutic anti-Xa levels.

Utilizing enoxaparin 0.5 mg/kg Q12h in all patients, regardless of weight, is likely to result in more in-target anti-Xa levels.

The correlation between anti-Xa levels and VTE is still unclear.
Drug Interactions Between Inhaled/Nasal or Intra-Articular Corticosteroids and Antiretrovirals (ARV)

Jillian Stanton, PharmD.
PGY1 Pharmacy Practice Resident
Virginia Commonwealth University Health System
Disclosures

- I currently have no disclosures to report
Learning Objectives

- Identify patients at risk for a clinically significant drug-drug interaction between ritonavir- or cobicistat-boosted ARV regimens and inhaled/nasal or intra-articular corticosteroids.

- Prepare a treatment recommendation for HIV-positive patients requiring ARV therapy and non-oral corticosteroids.
Patient Case: TC

- 67 y/o WM with HIV presenting for a routine follow up appointment today

Interval History

- HIV diagnosis: 2010
- Started on antiretrovirals in October 2013
- Hospitalized March 27-30, 2015 for a significant asthma attack
  - Pulse prednisone
  - Discharged on
    - Fluticasone-salmeterol
    - Insulin glargine
Patient Case: TC

- Home Medications:
  - Atazanavir 300 mg PO daily
  - Ritonavir 100 mg PO daily
  - Emtricitabine-tenofovir (200 mg/300 mg) PO daily
  - Fluticasone-salmeterol (200 mcg/50 mcg) inhalation BID
  - Insulin glargine 10 units SQ injection at bedtime
Patient Case: TC

Which drug combination is contributing to TC's elevated blood sugars?

A. Ritonavir and atazanavir
B. Fluticasone-salmeterol and ritonavir
C. Fluticasone-salmeterol and emtricitabine-tenofovir
D. Fluticasone-salmeterol and atazanavir
# Inhaled Fluticasone and Ritonavir

## Design
- Multiple-dose, crossover interaction study

## Population
- 18 healthy volunteers

## Intervention
- All subjects received:
  - Fluticasone propionate nasal (200 mcg) daily for 7 days
  - Fluticasone propionate nasal (200 mcg) daily for 7 days plus ritonavir 100 mg twice daily for 7 days

## Primary Outcome
- Average fluticasone $C_{\text{max}}$ and AUC

## Results
- **Fluticasone only:**
  - $C_{\text{max}} = 11.9 \text{ pg}\cdot\text{hr}/\text{mL} (10.8 \text{ to } 14.1 \text{ pg}\cdot\text{hr}/\text{mL})$
  - AUC = 8.43 pg•hr/mL (4.2 to 18.8 pg•hr/mL)
- **Fluticasone + Ritonavir:**
  - $C_{\text{max}} = 318 \text{ pg}\cdot\text{hr}/\text{mL} (110 \text{ to } 648 \text{ pg}\cdot\text{hr}/\text{mL})$
  - AUC = 3,102.6 pg•hr/mL (1,207.1 to 5,662 pg•hr/mL)

## Conclusions
- A significant increase in fluticasone propionate exposure which resulted in an 86% reduction in serum cortisol concentrations
**Inhaled Fluticasone and Ritonavir**

<table>
<thead>
<tr>
<th>Design</th>
<th>Multiple-dose, crossover interaction study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>18 healthy volunteers</td>
</tr>
<tr>
<td>Intervention</td>
<td>All subjects received:</td>
</tr>
<tr>
<td></td>
<td>• Fluticasone propionate nasal (200 mcg) daily for 7 days</td>
</tr>
<tr>
<td></td>
<td>• Fluticasone propionate nasal (200 mcg) daily for 7 days <strong>plus</strong> ritonavir 100 mg twice daily for 7 days</td>
</tr>
<tr>
<td>Primary Outcome</td>
<td>Average fluticasone $C_{\text{max}}$ and AUC</td>
</tr>
<tr>
<td>Results</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Fluticasone + Ritonavir:</strong></td>
</tr>
<tr>
<td></td>
<td><strong>GMR $C_{\text{max}}$ ↑ 26 times (Day 14 : Day 7)</strong></td>
</tr>
<tr>
<td></td>
<td><strong>GMR AUC ↑ 367 times (Day 14 : Day 7)</strong></td>
</tr>
<tr>
<td>Conclusions</td>
<td>• A significant increase in fluticasone propionate exposure which resulted in an 86% reduction in serum cortisol concentrations</td>
</tr>
</tbody>
</table>
Inhaled/Nasal Corticosteroids and ARVs

- Ritonavir and Cobicistat
  - *Strong CYP3A4 inhibitors*

- Inhaled/nasal Corticosteroids
  - *CYP3A4 substrates*
Clinical Evidence

- 51 case reports published between 1999 and 2012
- Corticosteroids
  - 91% fluticasone
  - 9% budesonide
- Time to onset was highly variable
- Associated consequences
  - Cushing’s disease
  - Adrenal insufficiency
- Time to resolution
  - 12.1 weeks (2-24 weeks)

Signs and Symptoms of Cushing’s

- Abnormal fat distribution
  - Buffalo neck
  - Moon facies
  - Facial atrophy
- Increased body weight
- Proximal myopathy
- Cutaneous changes
  - Abdominal stretch
  - Fragility, ecchymosis, purpura

- Hyperandrogenism
  - Hirsutism
  - Acne
  - Oligomenorrhea, amenorrhea
- Hypertension
- Emotional changes
- Impaired glucose tolerance
- Osteoporosis

Management

- Discontinue inhaled/nasal corticosteroid

- Follow patient closely to monitor for Cushing’s disease or adrenal insufficiency

- Consider lower risk corticosteroids
Management

<table>
<thead>
<tr>
<th>Inhaled Corticosteroid</th>
<th>Metabolism</th>
<th>Receptor Binding Affinity (Dexamethasone= 100)</th>
<th>Protein Binding (%)</th>
<th>Lipophilicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beclomethasone dipropionate</td>
<td>Esterase and CYP3A4</td>
<td>43</td>
<td>87</td>
<td>1.3</td>
</tr>
<tr>
<td>Budesonide</td>
<td>CYP3A4</td>
<td>855</td>
<td>85-90</td>
<td>1.9</td>
</tr>
<tr>
<td>Fluticasone propionate</td>
<td>CYP3A4</td>
<td>1910</td>
<td>99</td>
<td>3.4</td>
</tr>
<tr>
<td>Fluticasone furoate</td>
<td>CYP3A4</td>
<td>2990</td>
<td>99</td>
<td>No Data</td>
</tr>
<tr>
<td>Flunisolide</td>
<td>Glucuronidation/sulfation</td>
<td>180</td>
<td>80</td>
<td>1.1</td>
</tr>
<tr>
<td>Mometasone furoate</td>
<td>CYP3A4</td>
<td>2200</td>
<td>98.5</td>
<td>3.4</td>
</tr>
</tbody>
</table>

## Management

<table>
<thead>
<tr>
<th>Inhaled Corticosteroid</th>
<th>Metabolism</th>
<th>Receptor Binding Affinity (Dexamethasone= 100)</th>
<th>Protein Binding (%)</th>
<th>Lipophilicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beclomethasone dipropionate</td>
<td>Esterase and CYP3A4</td>
<td>43</td>
<td>87</td>
<td>1.3</td>
</tr>
<tr>
<td>Budesonide</td>
<td>CYP3A4</td>
<td>855</td>
<td>85-90</td>
<td>1.9</td>
</tr>
<tr>
<td>Fluticasone propionate</td>
<td>CYP3A4</td>
<td>1910</td>
<td>99</td>
<td>3.4</td>
</tr>
<tr>
<td>Fluticasone furoate</td>
<td>CYP3A4</td>
<td>2990</td>
<td>99</td>
<td>No Data</td>
</tr>
<tr>
<td>Flunisolide</td>
<td>Glucurunidation/ sulfation</td>
<td>180</td>
<td>80</td>
<td>1.1</td>
</tr>
<tr>
<td>Mometasone furoate</td>
<td>CYP3A4</td>
<td>2200</td>
<td>98.5</td>
<td>3.4</td>
</tr>
</tbody>
</table>

Management

<table>
<thead>
<tr>
<th>Design</th>
<th>Open label, prospective, randomized PK/PD study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>30 healthy volunteers aged 18-60 with no underlying medical conditions</td>
</tr>
<tr>
<td>Intervention</td>
<td>Volunteers all received beclomethasone dipropionate (BDP) for 14 days and were randomized into 3 groups:</td>
</tr>
<tr>
<td></td>
<td>• Control: BDP alone for 28 days</td>
</tr>
<tr>
<td></td>
<td>• BDP + ritonavir 100mg BID for 28 days</td>
</tr>
<tr>
<td></td>
<td>• BDP + darunavir/ritonavir (600/100) BID for 28 days</td>
</tr>
<tr>
<td>Primary Outcome</td>
<td>Geometric mean ratios of BDP in the blood (day 28: day 14)</td>
</tr>
<tr>
<td>Results</td>
<td>Control: 0.93 (0.81-1.06, p=0.61)</td>
</tr>
<tr>
<td></td>
<td>BDP + ritonavir: 2.08 (1.52-2.65, p=0.006)</td>
</tr>
<tr>
<td></td>
<td>BDP + darunavir/ritonavir: 0.89 (0.68-1.09, p=0.61)</td>
</tr>
<tr>
<td></td>
<td>There were no significant differences in serum cortisol levels at day 14, 28 or 42 between the groups</td>
</tr>
<tr>
<td>Conclusions</td>
<td>Darunavir/ritonavir did not increase exposure to 17-BDP but ritonavir alone did. Serum cortisol concentrations remained the same.</td>
</tr>
</tbody>
</table>
Which drug combination is contributing to TC’s elevated blood sugars?

A. Ritonavir and atazanavir
B. Fluticasone-salmeterol and ritonavir
C. Fluticasone-salmeterol and emtricitabine-tenofovir
D. Fluticasone-salmeterol and atazanavir
Patient Case: TC

Which drug combination is contributing to TC’s elevated blood sugars?

A. Ritonavir and atazanavir

B. Fluticasone-salmeterol and ritonavir

C. Fluticasone-salmeterol and emtricitabine-tenofovir

D. Fluticasone-salmeterol and atazanavir
Patient Case: MN

- 60 y/o AAF with HIV and osteoarthritis (OA) presenting for assistance in ART adherence

- **Current ART regimen:**
  - Darunavir/cobicistat 800 mg/150 mg PO once daily
  - Emtricitabine/ tenofovir 200 mg/ 300 mg PO daily
Patient Case: MN

Patient reveals that she has been getting corticosteroid injections for treatment of OA. Her last injection was 4/8/2014.

How would you respond?

A. Since corticosteroid injections are localized, there is no risk of corticosteroid toxicity
B. Cobicistat does not have the same risks as ritonavir, there is no risk of corticosteroid toxicity
C. Switch patient to a non-PI/ cobicistat regimen
D. Continue current ART regimen and monitor closely
Clinical Evidence: Intra-articular Corticosteroids

- 11 case reports published since 2008
- All patients received at least one injection of triamcinolone acetonide and 100-200 mg of ritonavir daily
- Consequences
  - 2 patients developed avascular necrosis
  - Most patients developed Cushing’s disease with subsequent adrenal insufficiency
- Time to recovery
  - Minimum of 3 months

Wood B. JIAPAC 2015; 8: 113-121.
Management

- If the patient has not yet received the injection, is it necessary?
- Consider switching patient to a PI- or cobicistat-sparing regimen
- Carefully monitor for signs and symptoms of Cushing’s syndrome
  - A morning cortisol and ACTH concentration to assess for adrenal suppression
  - Physiologic doses of glucocorticoid replacement with hydrocortisone may be necessary
- *Education and prevention is key*

Patient Case: MN

- Patient reveals that she has been getting corticosteroid injections for treatment of OA. Her last injection was 4/8/2014.

- How would you respond?
  A. Since corticosteroid injections are localized, there is no risk of corticosteroid toxicity
  B. Cobicistat does not have the same risks as ritonavir, there is no risk of corticosteroid toxicity
  C. Switch patient to a non-PI/ cobicistat regimen
  D. Continue current ART regimen and monitor closely
Patient Case: MN

- Patient reveals that she has been getting corticosteroid injections for treatment of OA. Her last injection was 4/8/2014.

- How would you respond?
  A. Since corticosteroid injections are localized, there is no risk of corticosteroid toxicity
  B. Cobicistat does not have the same risks as ritonavir, there is no risk of corticosteroid toxicity
  C. Switch patient to a non-PI/ cobicistat regimen
  D. Continue current ART regimen and monitor closely
Key Points

- Avoid the combination of ritonavir- or cobicistat-boosted ARV regimens with:
  - Inhaled corticosteroids
  - Intranasal corticosteroids
  - Intra-articular corticosteroids

- Consider alternative options when possible
  - Change patients to a non boosted ARV regimen
  - Selecting a lower risk steroid
Drug Interactions Between Inhaled/Nasal or Intra-Articular Corticosteroids and Antiretrovirals (ARV)

Jillian Stanton, PharmD.
PGY1 Pharmacy Practice Resident
Virginia Commonwealth University Health System
This is Your Brain. This is Your Brain on Sugar.

A Pharmacist’s Guide to the Ketogenic Diet

Kaitlin Pruskowski, PharmD.
PGY1 Pharmacy Resident
Johns Hopkins Bayview Medical Center
I have no relevant financial relationships or commercial interests to disclose for this presentation.
Objectives

• Define the ketogenic diet and its components
• Develop a therapeutic plan for patients who are on the ketogenic diet, considering drug delivery and adverse effects
Background

- Historical treatment option for epilepsy
- Fell out of favor as AEDs were developed
- Used for refractory epilepsy
  - Multidisciplinary approach required

Principles of the Ketogenic Diet

<table>
<thead>
<tr>
<th>Lipids (g):Non-lipids (g)</th>
<th>3:1 in infants, adolescents, and adults 4:1 in all other children</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluids</td>
<td>As low as 80% daily requirement</td>
</tr>
<tr>
<td>Calories</td>
<td>75% of daily requirement; can be modified if needed</td>
</tr>
<tr>
<td>Carbohydrates</td>
<td>Adults: &lt;15-20g per day</td>
</tr>
</tbody>
</table>

## Adult Diet Comparison

<table>
<thead>
<tr>
<th>4:1 Ketogenic Diet</th>
<th>USDA Dietary Guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td>• 2000 calories</td>
<td>• 2000 calories</td>
</tr>
<tr>
<td>• Fat 200g</td>
<td>• Fat 65g</td>
</tr>
<tr>
<td>• Carbohydrate 14g</td>
<td>• Carbohydrate 300g</td>
</tr>
<tr>
<td>• Protein 36g</td>
<td>• Protein 54g</td>
</tr>
</tbody>
</table>

USDA. Dietary guidelines for adults. 2010.
Additional Nutritional Supplementation

Universal
- Multivitamin + minerals and trace elements
- Calcium + vitamin D

As Needed
- Selenium
- Magnesium
- Zinc
- Phosphorous
- Carnitine

Adverse Effects of the Ketogenic Diet

**Short-Term**
- Dehydration
- Hypoglycemia
- Hypokalemia
- Lethargy
- Constipation
- GERD

**Long-Term**
- Failure to thrive
- Hemolytic anemia
- Osteopenia
- Nephrolithiasis
- Dyslipidemia

# Adverse Effects with Concurrent Valproic Acid

<table>
<thead>
<tr>
<th>Adverse Effect</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Hypokalemia</td>
<td>• KCl supplementation</td>
</tr>
<tr>
<td>• Hypoalbuminemia</td>
<td>• Increase protein intake to 2.25 g/kg/day</td>
</tr>
<tr>
<td>• Increased Scr</td>
<td>• Oral rehydration</td>
</tr>
<tr>
<td>• Renal tubular acidosis</td>
<td>• Polycitra-K and bicarbonate supplementation</td>
</tr>
<tr>
<td>• Microvascular steatosis</td>
<td>• Valproic acid discontinued</td>
</tr>
<tr>
<td>• Increased LFTs</td>
<td>• Valproic acid discontinued</td>
</tr>
</tbody>
</table>

# Adverse Effects with Concurrent Topiramate

<table>
<thead>
<tr>
<th>Adverse Effect</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Metabolic acidosis</td>
<td>• $\text{HCO}_3^-$ supplementation may be required</td>
</tr>
<tr>
<td>• Nephrolithiasis</td>
<td>• Maximize fluid intake</td>
</tr>
<tr>
<td></td>
<td>• Citrate supplementation may be required</td>
</tr>
</tbody>
</table>

Determining Carbohydrate Content of Medications

• Carbohydrate content comes from excipients, not the drug itself
• Carbohydrate content depends on the product and manufacturer
• Manufacturers may have information on carbohydrate contents
• Ketogenic diet centers may have product-specific carbohydrate content data
Drug Delivery Considerations

• Oral considerations
  – Oral liquids contain significantly more carbohydrates than tablets or capsules

• IV considerations
  – Dextrose solutions should be avoided
  – Patients may be on fluid-restriction as part of the ketogenic diet

• Compounded products
  – Avoid simple syrup and flavored syrups
  – Sugar-free Ora-Sweet and Ora-Blend are preferred
Which of the following are dietary restrictions of the ketogenic diet?

a) Fluid restriction
b) Calorie restriction
c) Carbohydrate restriction
d) Maintain lipid:non-lipid in a 4:1 ratio
e) All of the above
Which of the following drug dosage forms contain, on average, the highest amount of carbohydrates?

a) Tablets
b) Capsules
c) Oral liquids
d) Suppositories
Summary and Conclusions

• Ketogenic diet can be an alternative therapeutic option for patients with refractory epilepsy

• For the ketogenic diet to be effective, carbohydrate intake must be limited

• Pharmacists can help to manage and optimize pharmacotherapy for patients following the ketogenic diet by considering the carbohydrate content of medications when developing therapeutic regimens
References

This is Your Brain. This is Your Brain on Sugar.
A Pharmacist’s Guide to the Ketogenic Diet

Kaitlin Pruskowski, PharmD.
PGY1 Pharmacy Resident
Johns Hopkins Bayview Medical Center
Reaching for the stars?
Three ways pharmacists can help physician practices achieve quality measures and improve STAR ratings

Kirsten Garman, Pharm.D.
PGY-1 Pharmacy Practice Resident
Conemaugh Memorial Medical Center
Johnstown, Pennsylvania
No relevant financial relationships with commercial interests exist.
Learning Objectives

- To identify three ways pharmacists can help physician practices achieve quality measures and improve STAR ratings
- To identify a new reimbursement mechanism for pharmacists in the ambulatory care setting
Educational Needs Assessment

- Achieving quality measures set by a Medicare Advantage plan improves a physician practice’s STAR rating and increases reimbursement
- Pharmacists can greatly contribute by actively engaging themselves in a physician practice
Highmark Quality Blue Project

- Recognizes and financially rewards PCPs who work collaboratively with Highmark
- Measured on quality and operational efficiency indicators
- Evidence-based care in accordance with nationally recognized guidelines and benchmarks
Annual Wellness Visits (AWV)
AWV Components: History

- Medical, surgical, family history
- Medications, supplements, and allergies
- Lifestyle assessment
  - Smoking status
  - Physical activity
  - Diet
- Review of potential risk for depression
- Review of functional ability and level of safety
AWV Components: Examination

- Height, weight, BMI, blood pressure
- List of other providers
- Assessment of cognitive function
AWV Components: Counseling

- Written screening schedule and recommended preventive services
- List of risks and recommendations
- Referrals to programs, as appropriate
# Healthcare Common Procedure Coding System (HCPCS) Codes

<table>
<thead>
<tr>
<th>HCPCS Code</th>
<th>Code Descriptor</th>
</tr>
</thead>
<tbody>
<tr>
<td>G0402</td>
<td>Initial Preventative Physical Examination</td>
</tr>
<tr>
<td>G0438</td>
<td>Annual wellness visit, includes a Personalized Prevention Plan of Service (PPPS), initial visit</td>
</tr>
<tr>
<td>G0439</td>
<td>Annual wellness visit, includes a Personalized Prevention Plan of Service (PPPS), subsequent visit</td>
</tr>
</tbody>
</table>
Diabetes Care
Diabetes Care

- C04: Comprehensive Diabetes Care:
  - LDL-C Screening
- C15: Comprehensive Diabetes Care:
  - Eye exam (retinal) performed
- C16: Comprehensive Diabetes Care:
  - Medical attention for nephropathy
- C17: Comprehensive Diabetes Care:
  - HbA1c Control (≤9%)
- C18: Comprehensive Diabetes Care:
  - LDL-C Control (<100 mg/dL)
Medication Adherence

- D13: Medication adherence for diabetes
- D14: Medication adherence for hypertension
  - Renin angiotensin aldosterone system (RAAS) agents
- D15: Medication adherence for cholesterol
  - Statin
High Risk Medications
High Risk Medications

- D11: High risk medications in the elderly
- 66 years of age and older
- List of medications provided
  - Digoxin (>125 mcg/day)
  - Amitriptyline
  - Eszopiclone, zaleplon, zolpidem (continuous supply >90 days)
- Recommend to discontinue or taper medication
- Provide alternatives to therapy
Case Study

- 71 yo F with a PMH significant for T2DM, atrial fibrillation, HPL, and HTN

- Medications: metformin 1000 mg PO BID, metoprolol 25 mg PO BID, digoxin 250 mcg PO daily, pravastatin 40 mg PO daily, and lisinopril 10 mg PO daily

- Labs:
  - A1c 10.3% (November 2014)
  - LDL-C 104 mg/dL (August 2014)
  - SCr 1.1 (March 2015)
Drug Therapy Problems & Interventions

- A1c >9%
  - Recommend initiating basal insulin or addition of 1-2 oral agents
- LDL >100 mg/dL
  - Calculate ASCVD risk
  - Recommend appropriate therapy and monitoring
- High risk medication: digoxin >125 mcg/day
  - Calculate CrCl
  - Recommend dose reduction and monitoring
Additional Interventions

- Scan EMR for ophthalmology report
  - Remind patient if annual eye exam has not been completed
- Determine medication nonadherence
  - Call patient to discuss nonadherence issues
True or False:

Pharmacists, under the direct supervision of a physician, are allowed to perform the Medicare Annual Wellness Visit.

TRUE
Pharmacists can contribute to quality measure achievement by:

- Facilitating annual wellness visits
- Providing recommendations to physicians regarding drug therapy
- Contacting patients to address medication nonadherence
References


Questions?
New School Indication for an Old School Drug: Sub-dissociative ketamine for acute pain management in the Emergency Department

Amber Chiplinski Pharm.D., BCPS
Emergency Medicine Clinical Pharmacy Specialist
Meritus Medical Center
Hagerstown, MD
Amber.chiplinski@meritushealth.com
Conflict of Interest

- Nothing to disclose
Objectives

- Identify the appropriate population in which low dose ketamine is suitable for acute pain management
- Formulate a recommendation for dosing and side effect management strategies for use of low dose ketamine for acute pain management
Sub-dissociative doses of ketamine offer an alternate analgesic therapy that will not depress respiratory drive or hemodynamics.

Ketamine is an attractive agent for Emergency Department (ED) physicians as it also serves as an anxiolytic and antiemetic.

Ketamine provides another option pain management for patients that are otherwise tolerant or inappropriate for traditional therapy.
Old School

- Induction and maintenance of anesthesia
- Conscious sedation

- Dosing
  - IV: 1-4 mg/kg
  - IM: 2-10 mg/kg
Ketamine

- NMDA antagonist
  - Amnesia, psych, and analgesic effects
- Mu, delta, kappa opioid agonist/nicotinic & muscarinic antagonist
  - Psychiatric phenomenon
- Promotes adrenergic output
- Inhibits dopamine & serotonin uptake
- Pharmacokinetics
  - Onset 2-3 min, peak 30 min
  - Duration ~5 hours
  - Majority metabolized via liver
  - $t_{1/2}$ 2-3 hours

- Benefits
  - No compromise of airway
  - Hemodynamics stimulated
  - Anxiolysis/antiemetic
New School

- Post operative
  - Opioid PCA + ketamine $\rightarrow$ reduced pain scores, opioid use, desaturation

- Intractable cancer pain
  - Decreased opioid use

- Trauma
  - Better pain relief
  - Less opioid use and nausea/vomiting
  - Decreased LOS
2012 RCT evaluated use of morphine v. morphine + ketamine in the field by EMS for trauma

- 136 trauma patients with pain score > 5
- Morphine 5mg, then 1-5mg Q5min PRN + ketamine 10-20mg, then 10mg Q3min PRN
  - Vs. morphine alone
- Ketamine group had mean pain score decrease of 5.6 v. 3.2
- HTN, dysphoria, hallucinations, and GCS < 13 in 39% of ketamine group v. 14%
- Nausea/vomiting 2x frequent in morphine only group
2006 PROSPECTIVE, RANDOMIZED, DOUBLE BLIND TRIAL WITH 73 TRAUMA PATIENTS WITH ACUTE, SEVERE PAIN

- Ketamine 0.2 mg/kg + morphine vs. morphine + placebo
  - Morphine 0.1 mg/kg, then 3mg Q5 min PRN

- Primary end point: morphine consumption @ 30 min
  - Less morphine use in ketamine group
    - 0.149 mg /kg (range 0.132-0.165) vs. 0.202 mg /kg (range 0.181-0.223), respectively (P < .001)

- The VAS score at 30 min did not differ significantly
2 MONTH NON-RANDOMIZED OBSERVATIONAL TRIAL IN 2012 EVALUATED 32 ED PATIENTS

- Pain score >5 due to various reasons
- IV ketamine 15mg + IV hydromorphone 0.5mg
  - Additional hydromorphone PRN

<table>
<thead>
<tr>
<th>Time</th>
<th>Patient Reports</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 min</td>
<td>93% reported at least 2 point decrease in pain score</td>
</tr>
<tr>
<td>15 min</td>
<td>67% had adequate pain relief and denied additional drug</td>
</tr>
<tr>
<td>30 min</td>
<td>30 min- 80% had some dissociative effect</td>
</tr>
</tbody>
</table>

- No cardiopulmonary events, HA, or hallucinations
- Overall, 90% said they would not be opposed to receiving the same therapy again
U.S. Military

- Used widely for battlefield analgesia and sedation
- Combat medics indicate ketamine > morphine/fentanyl for rapid relief of severe pain
- Analgesia

<table>
<thead>
<tr>
<th>Route</th>
<th>Dose</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV</td>
<td>0.1-0.5 mg/kg or 20mg</td>
<td>Q10 min PRN (until nystagmus occurs)</td>
</tr>
<tr>
<td>IM</td>
<td>0.4-1 mg/kg or 50-100 mg</td>
<td>Q30-60 min PRN</td>
</tr>
<tr>
<td>Intranasal</td>
<td>50 mg via atomizer</td>
<td>Q30-6 min PRN</td>
</tr>
</tbody>
</table>
Expert Opinion

- Presented at 2011 & 2013 ACEP Meeting
- Jim Ducharme, MD- McMaster School of Medicine
- 0.2-0.3 mg/kg IV followed by infusion of 0.1-0.3 mg/kg/hr IN ADDITION to an opioid
Considerations

- **Contraindications**
  - Age < 3 months
  - Hypertension
  - Elevated ICP/IOP
  - Psychiatric illness
  - Pregnancy/lactation
  - Ischemic heart disease
  - History of hallucinations
  - Allergy to ketamine

- **Side Effects**
  - Elevated HR & BP
  - Hypersalivation
  - Nausea
  - Muscular clonus
  - Nystagmus
  - Hallucinations
  - Nightmares
  - Emergence phenomenon
**Recommendations for Use**

- Adults age $\geq 18$ with moderate to severe pain refractory to opiates/NSAIDs or contraindication

- **Dosing**
  - IV: 0.1-0.5 mg/kg, max 20mg/dose, Q1H PRN

- Give with an opioid

- IV slow push


Gandy, J. Ketamine in Tactical Combat Casualty Care. DHB Decision Briefing.


The Drug Interaction Conundrum in the treatment of *Mycobacterium Avium Complex* disease (MAC) in HIV patients

Nandini Puranprashad, Pharm.D, AE-C
PGY-2 Ambulatory Care Resident
Bronx Lebanon Hospital
Email: npuranpr@bronxleb.org
Conflict of Interest Disclosures

Nandini Puranprashad, PharmD., AE-C

- I have no conflicts of interest to disclose
Objectives

• Review the treatment options of MAC therapy for HIV patients on antiretroviral therapy.

• Specify the common drug interactions associated with MAC therapy and antiretroviral therapy and recommend a treatment option that will minimize drug toxicity.
Patient Case

• RS is a 42 year old female patient
• Past medical history of AIDS (diagnosed in 2001) with CD4 count <20 cells/mm³ (02/27/15) and viral load of 226,047 copies/mL (01/26/15), weight 44.4kg
• Patient was last admitted to BLHC in November 2014, for failure to thrive and persistent fever
  – diagnosed with disseminated MAC
  – discharged on Clarithromycin 500mg 1 tab twice daily, Rifabutin 150mg 2 caps daily, and Ethambutol 400mg 2 tabs daily
• Patient was readmitted to Bronx Lebanon Hospital on 01/28/15 for fever
• Medical team continues MAC treatment but wants to restart antiretroviral therapy due to high HIV viral load
• The team decided to start patient on Stribild since patient prefers once a day dosing
Mycobacterium Avium Complex (MAC)

• Epidemiology
  – In absence of ART or chemoprophylaxis
    • Incidence of MAC is 20-40% in patients with low CD4+
  – With ART and chemoprophylaxis
    • Decreased to 2%
  – Commonly found in the environment (food and water)
    • Transmission: inhalation/ingestion/inoculation

Risk factors: plasma HIV RNA >100,000 copies/mL, prior opportunistic infections, previous colonization with MAC, CD4+ <50 cells/mm³
MAC: Diagnosis

- **Clinical presentation**
  - Gradual onset: fever, night sweats, weight loss, fatigue, diarrhea
  - In absence of ART, usually a disseminated multi-organ infection
  - Localized manifestations: lymphadenitis (cervical or mesenteric), pneumonitis, pericarditis, osteomyelitis, skin or soft tissue abscesses, genital ulcers, CNS infection

- **Laboratory abnormalities**
  - Anemia
  - Elevated liver alkaline phosphatase

Prophylaxis

- Recommended for patients with **CD4 < 50 cells/mm³**:  
  - Azithromycin 1200 mg PO once weekly *(AI)*  
  - Clarithromycin 500 mg PO BID *(AI)*  
  - Alternative is Rifabutin 300 mg PO daily *(BI)*  
    - Potential drug interactions *(ADJUST)*  
    - Must exclude active TB before starting

- Discontinue **primary prophylaxis** if responding to ART with increase **CD4 > 100 cells/mm³** for **3 months** *(AI)*
**Preferred Treatment Therapy**

At least 2 drugs as initial therapy *(AI)*:

- Macrolide plus ethambutol:
  - Clarithromycin 500 mg (7.5–15 mg/kg) twice daily *(AI)*
  - Alternative: Azithromycin 500–600 mg/day (10–20 mg/kg) *(AII)*

PLUS

- Ethambutol 15 mg/kg/day *(AI)*

---

**Chronic maintenance therapy/secondary prophylaxis *(AII)***

- Completed at least 12 months of therapy
- CD4 count is more than 100 cells/mm³ for 6 months
- No signs and symptoms of MAC disease
**Alternative Therapy**

Addition of a 3\(^{rd}\) or 4\(^{th}\) drug should be considered (CIII):

- CD4 less than 50 cells/mm\(^3\)
- High mycobacterial load (>2 log CFU/mL of blood)
- Not currently taking antiretrovirals

- **Rifabutin (Mycobutin)** 150–600 mg/day (CI)
  *(Rifabutin dose chosen on the basis of other antiretrovirals because of drug-drug interactions)*

- **Amikacin** 10-15mg/kg IV daily (CIII)
- **Streptomycin** 1gm IV/IM daily (CIII)
- **Ciprofloxacin** 500-750mg PO BID (CIII)
- **Levofloxacin** 500mg PO daily (CIII)
- **Moxifloxacin** 400mg PO daily (CIII)
Treatment failure

- Defined as lack of clinical response and positive blood cultures at 4-8 weeks post therapy
  - Susceptibility tests recommended
    - Resistance to macrolides more common with prior use
      - Not known if continuation of macrolide is beneficial if organism is resistant
  - **Bottom line:** ≥ 2 new agents started based on susceptibility
Rifabutin (RFB) with Antiretrovirals

<table>
<thead>
<tr>
<th>ARV</th>
<th>Can RFB be used?</th>
<th>RFB Dosing Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>NVP</td>
<td>Yes</td>
<td>No dose adjustment necessary</td>
</tr>
<tr>
<td>DLV</td>
<td>No</td>
<td>Contraindicated</td>
</tr>
<tr>
<td>EFV</td>
<td>Probably</td>
<td>RFB 450mg-600mg/d, EFV 600mg 3x/wk</td>
</tr>
<tr>
<td>ETR</td>
<td>Probably</td>
<td>RFB 300mg/d if no boosted PI</td>
</tr>
<tr>
<td>ATV/r</td>
<td>Yes</td>
<td>RFB 150mg QD or 300mg 3x/wk</td>
</tr>
<tr>
<td>FPV/r</td>
<td>Yes</td>
<td>RFB 150mg QD or 300mg 3x/wk</td>
</tr>
<tr>
<td>DRV/r</td>
<td>Yes</td>
<td>RFB 150mg QD or 300mg 3x/wk</td>
</tr>
<tr>
<td>IDV/r</td>
<td>Yes</td>
<td>RFB 150mg QD or 300mg 3x/wk</td>
</tr>
<tr>
<td>LPV/r</td>
<td>Yes</td>
<td>RFB 150mg QD or 300mg 3x/wk</td>
</tr>
<tr>
<td>SQV/r</td>
<td>Yes</td>
<td>RFB 150mg QD or 300mg 3x/wk</td>
</tr>
<tr>
<td>TPV/r</td>
<td>Yes</td>
<td>RFB 150mg QD or 300mg 3x/wk</td>
</tr>
<tr>
<td>MVC</td>
<td>Yes</td>
<td>MVC 300mg BID if no strong inducer or inhibitor; 150mg BID if strong inhibitor</td>
</tr>
</tbody>
</table>

Rifabutin 150mg three times weekly in combination with LPV/r has resulted in inadequate rifabutin levels and has led to acquired rifamycin resistance in patients with HIV-associated tuberculosis. Pharmacokinetic data reported in this table are results from healthy volunteer studies.

Therapeutic drug monitoring for rifabutin is recommended.
<table>
<thead>
<tr>
<th>Combination Drugs</th>
<th>Drug Interaction with MAC therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Atripla® (FTC 200mg + TDF 300mg + EFV 600mg): 1 tablet once daily</strong></td>
<td>RFB 450mg-600mg/d, EFV 600mg 3x/wk</td>
</tr>
<tr>
<td><strong>Combivir® (ZDV 300mg + 3TC 150mg): 1 tablet BID</strong></td>
<td>No known interaction</td>
</tr>
<tr>
<td><strong>Epzicom® (ABC 600mg + 3TC 300mg): 1 tablet once daily</strong></td>
<td>No known interaction</td>
</tr>
<tr>
<td><strong>Trizivir® (ABC 300mg + ZDV 300mg + 3TC 150mg): 1 tablet BID</strong></td>
<td>No known interaction</td>
</tr>
<tr>
<td><strong>Truvada® (FTC 200mg + TDF 300mg): 1 tablet once daily</strong></td>
<td>No known interaction</td>
</tr>
<tr>
<td><strong>Complera® (FTC 200mg + TDF 300mg + RPV 25mg) 1 tab daily</strong></td>
<td>Increase the rilpivirine adult dose to 50 mg/day in patients during concomitant treatment with rifabutin</td>
</tr>
<tr>
<td><strong>Stribild® (Elvitegravir 150mg + Cobicistat 150mg + FTC 200mg + TDF 300 mg) 1 tab daily</strong></td>
<td>AVOID</td>
</tr>
<tr>
<td><strong>Triumeq (Abacavir / Dolutegravir / Lamivudine) 1 tab daily</strong></td>
<td>No known interaction</td>
</tr>
<tr>
<td><strong>Evotaz (Atazanavir / Cobicistat) 1 tab daily</strong></td>
<td>RFB 150mg QOD or 3x/wk</td>
</tr>
<tr>
<td><strong>Prezcobix (Darunavir / Cobicistat) 1 tablet daily</strong></td>
<td>RFB 150mg QOD or 3x/wk</td>
</tr>
</tbody>
</table>
# Antimycobacterials and Stribild Drug Interaction

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Combination Medication</th>
<th>Effect on Concomitant Drug Concentrations</th>
<th>Dosing Recommendations and Clinical Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rifabutin</td>
<td>EVG/cobi/TDF F/FTC</td>
<td>Compared with rifabutin (300 mg daily) administered alone, when rifabutin (150 mg every other day) administered with EVG/cobi/TDF/FTC, no significant change in rifabutin AUC; For 25-O-desacetyl-rifabutin, AUC ↑ 625% EVG AUC ↓ 21%, Cmin ↓ 67%</td>
<td>Do not co-administer</td>
</tr>
</tbody>
</table>
| Clarithromycin | EVG/cobi/TDF F/FTC | ↑ clarithromycin possible ↑ cobi possible | CrCl ≥60 mL/min:  
- No dose adjustment is necessary.  
CrCl 50–60 mL/min:  
- Reduce clarithromycin dose by 50%.  
CrCl <50 mL/min:  
- EVG/cobi/TDF/FTC is not recommended |
Patient Case

• Pharmacy notified the medical team of Stribild drug interaction with Rifabutin
  ➢ recommended to substitute rifabutin with an alternative agent or change to another antiretroviral medication

• Infectious Diseases team was consulted
  ➢ recommended to keep MAC therapy and start emtricitabine 200mg/rilpivirine 25mg/tenofovr 300mg (Complera)

• Pharmacy notified the team of interaction with Complera and rifabutin
  ➢ rilpivirine dose has to be 50 mg/day with coadministration of rifabutin
  ➢ an additional rilpivirine 25mg tablet must be given with Complera while patient is taking rifabutin

• Patient’s new viral load is 219 copies/mL (03/05/15)
Clinical Pearls

• When treating MAC: *use at least 2 agents based on susceptibility*

• Minimum treatment time is *at least 12 months of therapy*
  - Then discontinue if CD4 count is > 100 cells/mm$^3$ for 6 months and no signs and symptoms of MAC disease

• For patients newly infected with MAC already on active antiretrovirals
  - Use alternative MAC therapy to avoid drug interactions

• For MAC patients NOT on antiretroviral
  - Start MAC therapy and initiate antiretroviral therapy 2 weeks later to avoid IRIS
  - Always check for drug interactions when recommending an antiretroviral agent
    - antiretroviral packet insert
    - AIDSinfo Guidelines for the Use of Antiretroviral Agents in HIV Infected Patients: http://aidsinfo.nih.gov/guidelines
  - AVOID the combination Rifabutin and Stribild
1. Which of the following MAC treatment regimen has the strongest recommendation for treating patients with CD4 less than 50 cells/mm$^3$, high mycobacterial load, and not on antiretroviral therapy?

a. Clarithromycin 500 mg twice daily + Ethambutol 15 mg/kg/day

b. Clarithromycin 500 mg twice daily + Ethambutol 15 mg/kg/day + Rifabutin 300mg daily

c. Azithromycin 600 mg daily + Ethambutol 15 mg/kg/day

d. Azithromycin 600 mg daily + Ethambutol 15 mg/kg/day + Levofloxacin 500mg daily
2. Which of the following HIV combination regimen does not have a drug interaction warning with MAC treatment therapy?
   a. Atripla
   b. Stribild
   c. Evotaz
   d. Truvada
Aspiration Pneumonia vs. Aspiration Pneumonitis – Can Serum Procalcitonin Levels Give Us the Answer?

Samantha Formeck, PharmD
PGY1 Pharmacy Practice Resident
Conemaugh Memorial Medical Center
Disclosures

- There is no commercial support or financial relationships associated with this educational activity.
- I disclose no relationship with any commercial company.
Objectives

- To distinguish between aspiration pneumonia and aspiration pneumonitis
- To identify the biomarker for bacterial infection that has been used successfully to guide antibiotic use
Pulmonary Aspiration Syndromes

- Inhalation of either oropharyngeal or gastric contents into the lower airways
- Aspiration Pneumonia
  - infectious process caused by the inhalation of secretions colonized by pathogenic bacteria
- Aspiration Pneumonitis
  - chemical injury caused by the inhalation of sterile gastric contents
Pulmonary Aspiration Syndromes

- Risk factors
  - Altered consciousness
  - Dysphagia
  - Endotracheal intubation

- Clinical presentation
  - Cough
  - Dyspnea
  - Severe hypoxemia
  - Infiltrates on chest radiograph
True or False?

- Both aspiration pneumonia and aspiration pneumonitis have similar clinical presentations

- True
- False
Importance of Distinguishing Between Aspiration Syndromes

- Similar clinical presentations
- Most patients with a suspected aspiration event are treated empirically with antibiotics
- Can lead to inappropriate antibiotic therapy
- Ultimately increases the risk of antibiotic resistance and potential adverse effects
“Antibiotics ‘Just-In-Case’ in a Patient with Aspiration Pneumonitis”

- 50 yo male admitted who presented to the ED with a witnessed generalized tonic-clonic seizure
- Completed 7 days of treatment with piperacillin/tazobactam for possible aspiration pneumonia
- Presented back to the hospital a week later and was treated for a severe Clostridium difficile infection
- Despite treatment, on day 18 of hospitalization he died of unresolving C. difficile colitis

Diagnostic Markers of Infection

- Erythrocyte sedimentation rate (ESR)
- C-reactive protein (CRP)
- White blood cell count (WBC)
- Procalcitonin (PCT)
Procalcitonin

- 116-amino acid prohormone of calcitonin
- Synthesized in response to lipopolysaccharides and bacterially-induced cytokines
- Significant role in the immune system’s pro-inflammatory response
- Has been used successfully to guide both the initiation and/or discontinuation of antibiotic therapy
Kinetic Profile of Procalcitonin

- Typically undetectable in healthy individuals
- Released into the bloodstream in the presence of a bacterial infection
- Correlates with severity and extent of infection
- Becomes detectable within four hours of initial host invasion
- Half-life of between 24-35 hours in the absence of an ongoing stimulus
Interpreting Serum Procalcitonin Results

- Normal ranges are not standardized
- Vary based on labs and clinical settings
- Most clinical trials utilize the following ranges:
  - $> 1 \text{ mcg/ml}$ - “high likelihood of infection”
  - $< 0.25 \text{ mcg/ml}$ - “low likelihood of infection”
  - $0.25 – 1 \text{ mcg/ml}$ - “indeterminate”
Advantages of Procalcitonin

- Interesting kinetic profile over time
  - Daily decrease of around 50% once the infection is controlled by the immune system
- Not influenced by systemic corticosteroids
- Potential ability to estimate both the likelihood of bacterial infection and severity of infection
Limitations of Procalcitonin

- Severe mechanical trauma
- Post-surgical trauma
- Severe burns
- Inflammation associated with “cytokine storms”
Applying Results to Clinical Practice

- Procalcitonin thresholds are often determined by the patient’s clinical status.
- In a severely ill patient, antibiotic therapy should not be delayed while awaiting a procalcitonin result.
- More useful to measure serial procalcitonin levels.
- Should only be used to support clinical judgment.
True or False?

- Procalcitonin is a biomarker for bacterial infection that has been used successfully to guide antibiotic use

  - True
  - False
Summary

- Both aspiration pneumonia and aspiration pneumonitis have similar clinical presentations.
- Procalcitonin has been used successfully to guide both the initiation and/or discontinuation of antibiotic therapy.
- Procalcitonin has the potential ability to estimate both the likelihood of bacterial infection and severity of infection.
- Procalcitonin should only be used to support clinical judgment.
References


Reaching for the Stars: How to guide your resident through the first publication

Angela Cheng, PharmD, BCPS
Clinical Pharmacy Manager
Montefiore Medical Center
Assistant Professor of Medicine
Albert Einstein College of Medicine
Bronx, New York
May 5, 2015
Disclosures

• There is no commercial support associated with this educational activity

• The presenter has no relationship with any commercial company
Objectives

• To identify various ways in which a preceptor can help residents to prepare a manuscript suitable for publication

• To describe various types of assistance that a preceptor can provide to residents during the publication process
Significance

• Writing can be a good learning experience
• Publication is a marker of academic success
• First publication is usually a challenge for new clinicians
• Successful writing is a disciplined and systematic process
• Preceptors play an important role in helping residents to publish their first manuscript
How do we start?

• Assist resident to identify:
  – Ideas or topics for publication
  – Type of publication to submit
  – Appropriate journal for submission

• Ensure careful appraisal of the literature

• Choose helpful team members

• Formulate an outline

• Set a time schedule!
The writing process

• Review drafts by sections
• Ensure appropriate content in each section
• Confirm correct data being presented
• Contribute to the interpretation of data
• Revise as needed
  – Macrostructure (e.g., organization, content, flow)
  – Microstructure (e.g., words, grammar, spelling)
• Adhere to author guidelines
• Set a date to submit paper!
Assessment #1

A preceptor can help the resident to prepare a manuscript suitable for publication by:

A. Identifying a target journal for submission
B. Ensuring appropriate content in each section of the paper
C. Contributing to the interpretation of data and the discussion section
D. All of the above
The publication process

• Assist residents to reply to reviewers’ comments
  – Respond positively, non-defensively, and in detail to reviewers’ comments
  – Provide thoughtful, well-argued, and reasoned responses
  – Make changes in line with the reviewers’ recommendations at every opportunity

The publication process – cont’d

• Assist residents to revise and resubmit the manuscript

• Oversee the galley proofreading process

• Respond to author queries

• Celebrate!
Assessment #2

A preceptor should assist the resident with all of the following EXCEPT:

A. Responding to reviewers’ comments
B. Revising and resubmitting manuscripts
C. Paying for open access fees
D. Proofreading the galley
References and additional resource list


