Drug Side Effects and Toxicity

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Disclosures

• None
No one is above suspicion.

Drug
Toxicity – Nausea and vomiting
Any Drug Can Cause a Rash
Isoniazid

• Role: primary drug, along with rifampin
• Action: inhibits cell wall synthesis
• Dosage: oral, IM, IV (in saline only)
• Dose: 300mg QD; 10-20mg/kg for peds
• Clearance: liver>>kidney
• Toxicity: Hepatitis, neuropathy
INH Drug Interactions

• Increased concentrations of:
  • Anticonvulsants
    • Phenytoin, Barbiturates
    • Warfarin

• Decreases concentrations
  • Azole antifungals

• Inhibits histaminase and monoamine oxidase

• INH absorption inhibited by aluminum
  • Avoid antacids containing aluminum
Rifampin

- **Role:** primary drug, along with INH
- **Action:** DNA – dependent RNA synthetase
- **Dosage:** oral, IV
- **Dose:** 600mg daily; 10-20mg/kg for peds
  - New treatment regimens are looking at 35mg/kg doses
- **Cleared:** liver >> kidneys
- **Toxicity:** hepatotoxicity, flu-like syndrome
Rifabutin

• Role: Used when concerned about drug-drug interactions
• Action: DNA-dependent RNA synthetase
• Dosage: Oral
• Dose: 300mg once daily
• Clearance: liver >> kidneys
• Toxicity: neutropenia, thrombocytopenia, uveitis
Rifamycin Toxicity

- Hematologic
- Hepatotoxicity
- Nephrotoxicity
- Hypersensitivity
- "Influenza syndrome"
- "Lupus syndrome"
  - Fever, Rash, Leukopenia, thrombocytopenia, arthralgias
- Nausea and vomiting
Rifabutin Toxicity

• Hepatitis
• Uveitis
• Arthritis
• Fever
• Thrombocytopenia, Leukopenia
• Drug induced lupus
• Nausea and vomiting
Case

• 55 y/o female started on INH, ethambutol, moxifloxacin and rifampin for pulmonary M. tuberculosis infection
• 2 month f/u shows WBC of 4.0
• What are your thoughts about the WBC?
• What should you do?
Case continued

• 3 month f/u shows WBC of 1.5 (ANC 0.5); Platelet ct. 128,000
• What would you do next?
Case

• 66 y/o male with Interstitial Pulmonary Fibrosis and bronchoscopy specimen is culture positive for M. tuberculosis seen at NJH. AFB smear negative. Requiring 6 liters of supplemental oxygen in Denver. Seen by ILD service and started on 40 mg of prednisone with minimal response at 2 weeks. Patient had been started on rifampin, ethambutol, INH, and streptomycin by ID physician and had been started on prednisone by pulmonary docs.

• Why might he not be responding to the prednisone?
Case continued

• Pt. with severe nausea, vomiting and weight loss 2 months into therapy with rifampin, ethambutol, INH, and SM.

<table>
<thead>
<tr>
<th>LFT's</th>
<th>5/23/11</th>
<th>6/27/11</th>
</tr>
</thead>
<tbody>
<tr>
<td>AST</td>
<td>32</td>
<td>129</td>
</tr>
<tr>
<td>AP</td>
<td>95</td>
<td>442</td>
</tr>
<tr>
<td>TB</td>
<td>0.5</td>
<td>0.9</td>
</tr>
<tr>
<td>ALT</td>
<td>20</td>
<td>121</td>
</tr>
</tbody>
</table>

What could be causing the LFT’s abnormalities?

Why might he not be responding to the prednisone with improved oxygenation?
Case

- Develops severe joint aches, in knees and elbows and terrible fatigue and malaise
- What are your thoughts?
Drug-Induced Lupus Syndrome Associated with Rifamycin Therapy

• 5 pts on rifamycin (3 RFB, 2 RIF) developed malaise, arthralgias/arthritis and edema 5-7 months after starting therapy
  • Rheum Hx: 1 prior drug induced lupus 4 yrs prior (INH Tx). 1 prior with Raynaud’s
  • All pts on Clari or other known hepatic enzyme inhibitors
  • All improved 1-10 weeks after D/C rifamycin

Pyrazinamide (PZA)

• Role: primary drug, first 2 months
• Action: affects fatty acid synthesis
• Dosage: oral
• Dose: 25-30mg/kg once daily (adults and peds)
• Cleared: liver, then metabolites via kidneys
• Toxicity: hepatotoxicity, elevated uric acid
Pyrazinamide (PZA)

• Hepatotoxicity
• Hyperuricemia (arthralgias)
• Gastrointestinal
• Hypersensitivity
Ethambutol (EMB)

- **Role:** Part of initial treatment regimen
- **Action:** inhibits cell wall synthesis
- **Dosage:** oral
- **Dose:** 15-25mg/kg once daily (adults and peds)
- **Cleared:** kidneys >> liver
- **Toxicity:** ocular toxicity, rashes
Case presentation

- 76 year old female continuing on Rifampin, Ethambutol, and levofloxacin for M. tuberculosis (INH induced hepatitis)
- 2 months later reported visual changes to local MD, but no med changes were made. Told her this was likely secondary to cataracts (known)
- What would you do in this situation?
Case presentation

• At 3 months, could not read newspaper; legally blind
• Vision returned to normal over 1 years, and doing fine 2 years later. Had cataracts removed later.
Ethambutol Optic Neuritis

... and now if you could close the other 650 eyes and read the bottom line....

Fly Hell.
Ethambutol Optic Neuritis
Ethambutol Optic Neuritis
Ethambutol Toxicity

- Optic Neuritis
- Hyperuricemia
- Peripheral Neuropathy
- Hypersensitivity
- Hair loss
Ethambutol Toxicity

• Different dosing regimens are used
• 25 mg/kg once daily x 2 months then decrease to 15 mg/kg daily to complete 18-24 months
• Griffith - Retrospective study of 229 patients Mean age 63.8; 55% women
  • 139 pts with daily therapy
  • Mean duration of EMB tx 16.1 months
  • EMB daily 25 mg/kg/d x 2 mos then 15 mg/kg day
  • 6% developed ocular toxicity

Ethambutol Toxicity

• None of the cases were detected by routine ocular exam
  • Ishihara vs. visual acuity vs. visual field testing
• Visual acuity returned to normal after discontinuation of EMB
• 90 patients received Mon, Wed, Fri therapy with 25 mg/kg
  • None had ocular toxicity
  • Cum dose of EMB in daily significantly higher (P=0.0001)
Ethambutol Monitoring

- Regular assessment of color and acuity
- Avoid use in children (NO!)
- Use with caution in renal failure
Ethambutol Induced Rash

• After a rash occurs, it is best to let things quiet down for 4 weeks
• Then you can consider desensitization to either/both ethambutol and rifampin
• Consider starting H1/H2 blocker (cetirizine/ranitidine) as soon as possible and you may need to use prednisone as well to help rash resolve

Streptomycin

• **Role:** “Fourth drug” in case of resistance
• **Action:** inhibits protein synthesis
• **Dosage:** IM, IV
• **Dose:** 12-15mg/kg once daily (adults and peds)
• **Cleared:** kidneys
• **Toxicity:** ototoxicity, nephrotoxicity, cation loss
Amikacin, Capreomycin, Kanamycin

• Role: Drug resistant TB
• Action: same as streptomycin
# Aminoglycosides

## Side Effects/Toxicity

<table>
<thead>
<tr>
<th>Side Effects/Toxicity</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Nephrotoxicity</td>
<td>• Electrolyte panel</td>
</tr>
<tr>
<td>• Ototoxicity</td>
<td>• Audiogram</td>
</tr>
<tr>
<td>• Vestibular toxicity</td>
<td>• Vestibular testing</td>
</tr>
<tr>
<td>• Electrolyte abnormality</td>
<td>• Replacement therapy</td>
</tr>
<tr>
<td>• Eosinophilia</td>
<td>• Not significant</td>
</tr>
<tr>
<td>• Local soreness</td>
<td>• Ultrasound, hot packs, lidocaine</td>
</tr>
</tbody>
</table>
Hearing Loss Monitoring

AUDIOGRAM

Hearing Level (dB)

Frequency (Hz)

125 250 500 1000 2000 4000 8000

z, v, f, s, th

Mild

m, n, g

Vowels

p, h, k

Dog barking

Loud shouting

Consonants

j, b, d, g

Telephone ringing

Lawn mower

Severe

f, s, th

Profound

Jackhammer, Firecracker, Gunshot

Hearing Range (with common hearing loss)
Other Aminoglycoside Effects

• Hypersensitivity
• Neurotoxicity
  • Circumoral paresthesias
  • Decreased mental concentration
  • Post operative respiratory depression
  • Drug induced myasthenia gravis
Other Aminoglycoside Effects

• Hematologic
  • Aplastic anemia
  • Agranulocytosis

• Drug Interactions
  • Heparin breaks down aminoglycosides \textit{in vitro}
Levofloxacin

• Role: drug resistant TB
• Action: inhibits DNA gyrase
• Dosage: oral, IV
• Dose: 750-1000mg once daily
• Cleared: kidneys
• Toxicity: caffeine like effects, GI, tendonitis
Moxifloxacin

• Action: inhibits DNA gyrase
• Dosage: oral, IV
• Dose: 400mg once daily
• Cleared: kidneys
• Toxicity: caffeine-like effects, GI, tendonitis, hypoglycemia
Case

- 65 y/o physician with MDRTB contracted while serving as a medical missionary in the Ukraine.
- Avid runner
- On Ethambutol, Amikacin, PAS, and Moxifloxacin
- 6 months into therapy begins to experience calf tightness after running
- What are your thoughts?
Ruptured Achilles Tendon

- Normal Achilles tendon
- Torn Achilles tendon
- Fluid
Prolonged QT interval – Quinolones, macrolides, clofazimine, bedaquiline
Quinolone Pearls

• Things to watch for with moxifloxacin
  • Best on empty stomach
  • Don’t take within 2 hours of calcium/magnesium/iron containing supplements or foods
  • Take in AM because of caffeine-like effects
  • Use with caution in the elderly because of CNS side effects, hypoglycemia, and tendonitis
Ethionamide

• Role: drug resistant TB
• Action: inhibits cell wall synthesis
• Dosage: oral
• Dose: 250-500mg BID; 10-20mg/kg divided BID for peds
• Cleared: liver
• Toxicity: GI upset, decreased thyroid function, decreased libido, and hyperglycemia
P-aminosalicylic Acid (PAS)

• Role: drug resistant Tb
• Action: not known
• Dosage: oral
• Dose: 4gm BID-TID
• Cleared: liver >> kidneys
• Toxicity: GI upset, increased flatulence, hypothyroidism
Case

• 26 year old female with MDRTB tx’d for 2 years with ethambutol, PAS, ethionamide, levofloxacin, and cycloserine.

• 4 weeks after completing therapy she has tachycardia, weight loss, “feels like she is going to die”

• What is going on?

• Heart rate is 130, diaphoretic, “panic” look

• TSH is 0.0

• She is HYPERTHYROID b/c physician forgot to d/c the synthroid that was started during treatment for HYPOTHYROIDISM caused by ethionamide and PAS.
Cycloserine

• Role: drug resistant TB
• Action: inhibits cell wall synthesis
• Dosage: oral
• Dose: 250-500mg BID; 10-20 mg/kg divided BID for peds
• Cleared: kidneys
• Toxicity: lack of concentration, altered behavior
“Psychoserine”
Therapeutic Drug Monitoring
## Therapeutic Drug Monitoring

<table>
<thead>
<tr>
<th>Drug</th>
<th>Treatment Details</th>
<th>Therapeutic Range</th>
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</thead>
<tbody>
<tr>
<td>INH</td>
<td>300mg daily</td>
<td>3 - 6 mcg/ml</td>
</tr>
<tr>
<td></td>
<td>900mg BIW</td>
<td>9 – 18 mcg/ml</td>
</tr>
<tr>
<td>Rifampin</td>
<td>600mg daily</td>
<td>8 – 24 mcg/ml</td>
</tr>
<tr>
<td>Rifabutin</td>
<td>300mg daily</td>
<td>0.3 – 0.9 mcg/ml</td>
</tr>
<tr>
<td>Rifapentine</td>
<td>600mg daily</td>
<td>8 – 30 mg/ml</td>
</tr>
<tr>
<td>PZA</td>
<td>35mg/kd daily</td>
<td>20— 50 mcg/ml</td>
</tr>
<tr>
<td></td>
<td>50mg/kg BIW</td>
<td>40 – 100 mcg/ml</td>
</tr>
</tbody>
</table>
## Therapeutic Drug Monitoring

<table>
<thead>
<tr>
<th>Drug Type</th>
<th>Dosage</th>
<th>Therapeutic Range</th>
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<tbody>
<tr>
<td>Ethambutol</td>
<td>25mg/kg daily</td>
<td>2 – 6 mcg/ml</td>
</tr>
<tr>
<td></td>
<td>50mg/kg BIW</td>
<td>4 – 12 mcg/ml</td>
</tr>
<tr>
<td>Aminoglycoside</td>
<td>15mg/kg daily</td>
<td>35 – 45 mcg/ml</td>
</tr>
<tr>
<td>(BIW)</td>
<td>22-25mg/kg</td>
<td>65 – 80 mcg/ml</td>
</tr>
</tbody>
</table>
Therapeutic Drug Monitoring

- Cycloserine: 20 – 35 mcg/ml
- Ethionamide: 1 – 5 mcg/ml
- PAS: 20 – 60 mcg/ml
- Ciprofloxacin: 4 – 6 mcg/ml
- Levofloxacin: 8 – 12 mcg/ml
- Clofazamine: 0.5 – 2 mcg/ml
Bedaquiline

• **CDC Recommendations – Dosing administration**
  - 400mg dose once daily for 2 weeks then lower to 200mg three times a week for an additional 22 weeks (DOT is mandatory!)
  - This antibiotic should only be used in combination with at least 3-4 other antibiotics to which laboratory tests indicate that the bacteria is susceptible

Mase S et al; MMWR; Oct. 25, 2013; 1-12
Bedaquiline

• **CDC Monitoring Recommendations**
  - Once a week, assess pt. for sxs of nausea, hemoptysis, chest pain, joint pain, and rash
  - Do an ECG **PRIOR TO** and again at 2, 12, and 24 weeks after treatment is started.
  - Monitor pts. For liver-related adverse drug reactions with serum transaminases
  - TDM should be considered in patients with severe renal impairment, or if it is being co-administered with other drugs that induce or suppress the cytochrome P450 system
  - May be used on case-by-case basis in children, HIV-infected persons, pregnant women, extrapulmonary MDR TB.
What drug caused this?
Treatment in Renal Failure

- **INH** - Decrease dose if severe, monitor drug concentrations
- **Rifampin** - No change
- **Ethambutol** - Reduce dose or increase intervals
- **Pyrazinamide** - Use with caution
- **Streptomycin** - Adjust dose according to concentrations
- **Cycloserine** - Monitor concentrations and CNS effects
Treatment in Pregnancy

- **INH** - Safe, give with pyridoxine
- **Rifampin** - Manufacturers caution, may be used safely
- **Ethambutol** - Safe
- **Pyrazinamide** - Little known
- **Aminoglycosides** - May cause CN 8 nerve toxicity, but may be necessary to use
- **Fluoroquinolones** - Avoid may cause fetal joint abnormalities
Great Sand Dunes National Park