Pharmacology of Anti-TB Medications

Vanessa Meyer, PharmD
March 18, 2015

TB Nurse Case Management
March 17-19, 2015
San Antonio, Texas

Vanessa Meyer, PharmD has the following disclosures to make:

• No conflict of interests
• No relevant financial relationships with any commercial companies pertaining to this educational activity
Anti-Tuberculosis Medications

Vanessa Meyer, PharmD

Objectives

- First-line anti-tuberculosis medications
- Second-line anti-tuberculosis medications
- New and investigational drugs
- Food-drug interactions
- Drug-drug interactions
FIRST-LINE ANTI-TUBERCULOSIS MEDICATIONS

* Not FDA approved for TB

**Rifampin, Rifabutin*, Isoniazid, Pyrazinamide, Ethambutol**

**Rifampin**

- **Dose**
  - Adults: 10 mg/kg/dose up to 600 mg (PO or IV)
  - Children: 10-20 mg/kg/dose up to 600 mg (PO or IV)

- **Administration**
  - Take 1 hour before or 2 hours after meals
  - Take 1 hour before antacids
  - Avoid alcohol
  - May mix the contents of capsule with applesauce or jelly
Rifampin

• Common side effects
  – Reddish-orange body fluids
    • Will stain contact lenses
  – Nausea/vomiting/diarrhea
  – Rash & pruritis
  – Increase in LFTs
  – Flu-like syndrome

• Serious adverse reactions
  – Hepatitis
  – Hematological (thrombocytopenia, hemolytic anemia)
  – Renal failure

Rifampin

• How supplied
  – Oral capsule: 150 mg, 300 mg
  – Injection, powder for reconstitution: 600 mg
  – Suspension available through compounding pharmacy
Rifampin

Rifampin 25 mg/ml Oral Suspension

Ingredients:
- 10 300 mg rifampin capsules
- 120 ml 1:4 cherry syrup concentrate/simple syrup

Directions:
1. Empty contents of 10 300 mg rifampin capsules in a mortar and triturate to a fine powder.
2. Wet powder with approximately 20ml of vehicle and mix until it is a uniform paste.
3. Continue adding vehicle geometrically until almost 120 ml.
4. Transfer to a graduated cylinder and rinse mortar with remaining vehicle.
5. Fill graduated cylinder to a total volume of 120 ml. Mix well.
6. Label with "shake well" and "refrigerate."

Total volume: 120 ml
Shelf life: 28 days refrigerated (preferred) or at room temperature

Rifabutin

- **Dose**
  - Adults: 5 mg/kg
  - Children: pediatric dose not established
    - 5-10 mg/kg/day have been used

- **Administration**
  - May be taken with or without food
Rifabutin

• Common side effects
  – Reddish-orange body fluids
  – Rashes and skin discoloration
    • Bronzing or pseudojaundice
  – Arthralgias

• Serious adverse reactions
  – Hepatotoxicity
  – Leukopenia/neutropenia
  – Anterior uveitis and other eye toxicities

Rifabutin

• How supplied
  – Capsule, oral: 150 mg
  – Suspension available through compounding pharmacy
Rifabutin

Rifabutin 20 mg/ml Oral Suspension

Ingredients:
- 8 Rifabutin 150 mg capsules
- 60 ml 1:1 Ora-Plus/Ora-Sweet

Directions:
1. Empty contents of 8 capsules into a glass mortar and triturate to a fine powder.
2. Wet powder with approximately 20 ml of vehicle and mix to a uniform paste.
3. Continue to mix and add vehicle geometrically to almost 60 ml.
4. Transfer to a graduated cylinder.
5. Rinse mortar with vehicle, and add to graduated cylinder.
6. Add vehicle to cylinder to make 60 ml. Stir well.
7. Add "shake well" label.

Total volume: 60 ml  Shelf life: 84 days at room temperature

Isoniazid

• Dose
  – Adults
    • 5 mg/kg/day
    • 20-30 mg/kg two to three times weekly
  – Children
    • 10-15 mg/kg/day
    • 20-30 mg/kg/dose two to three times weekly
Isoniazid

• Administration
  – Take 1 hour before or 2 hours after meals
  – May take with small snack if needed
  – Take 1 hour before or 2 hours after antacids
  – Supplement with pyridoxine if needed
  – Avoid alcohol
  – Avoid tyramine-containing foods
    • Aged cheese, tap/draft beers, sauerkraut, soy sauce

Isoniazid

• Common side effects
  – Peripheral neuropathy
    • Pyridoxine deficiency
  – Epigastric discomfort
  – Cramping with INH solution

• Serious adverse reactions
  – Hepatotoxicity
  – Hypersensitivity reactions

Images:
- Peripheral Neuropathy: http://avicennalaser.com/LaserTherapyFacts/Peripheral‐Neuropathy.htm
- Hepatitis C treatments: http://hepatitiscmx.com/hepatitis‐c‐treatments
Isoniazid

• How supplied
  – Injection, solution: 100 mg/mL
  – Solution, oral: 50 mg/5 mL in sorbitol
  – Tablet, oral: 100 mg, 300 mg

Pyrazinamide

• Dose
  – Adult:
  
<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>Daily Therapy</th>
<th>Twice Weekly DOT</th>
<th>Three/Week DOT</th>
</tr>
</thead>
<tbody>
<tr>
<td>40-55</td>
<td>1000 mg</td>
<td>2000 mg</td>
<td>1500 mg</td>
</tr>
<tr>
<td>56-75</td>
<td>1500 mg</td>
<td>3000 mg</td>
<td>2500 mg</td>
</tr>
<tr>
<td>76-90</td>
<td>2000 mg (maximum)</td>
<td>4000 mg (maximum)</td>
<td>3000 mg (maximum)</td>
</tr>
</tbody>
</table>

  – Children:
    • 15-30 mg/kg/daily
    • 50 mg/kg twice weekly

• Administration
  – May be taken with or without food

*based on lean body weight
Pyrazinamide

• Common side effects
  – Gout and arthralgias
    **Contraindicated in patients with severe gout**
  – Rash
  – Photosensitivity
  – Gastrointestinal upset

• Serious adverse reactions
  – Hepatitis


Pyrazinamide

• How supplied
  – Tablet, oral: 500 mg
  – Suspension available through compounding pharmacy

Images courtesy: www.epocrates.com and dailymed.nlm.nih.gov/dailymed
Pyrazinamide

Pyrazinamide 100 mg/ml Oral Suspension

<table>
<thead>
<tr>
<th>Ingredients:</th>
</tr>
</thead>
<tbody>
<tr>
<td>340  Pyrazinamide 500 mg tablets</td>
</tr>
<tr>
<td>850 ml Methylcellulose 1%</td>
</tr>
<tr>
<td>850 ml Simple Syrup</td>
</tr>
</tbody>
</table>

Directions:
1. Crush 200 Pyrazinamide 500 mg tablets.
2. Mix with a suspension containing 500 ml methylcellulose 1% and 500 ml simple syrup.
3. Crush 140 Pyrazinamide 500 mg tablets and mix with a suspension containing 350 ml methylcellulose 1% and 350 ml simple syrup.
4. Combine both suspensions to make 1.7 liter suspension.
5. Label “shake well” and “refrigerate.”

Total volume: 1.7 L
Shelf life: 60 days refrigerated or 45 days at room temperature

Ethambutol

- Dose
  - Adult
    - 15 mg/kg/day
    - 50 mg/kg twice weekly
  - Children
    - 15-20 mg/kg/day
    - 50 mg/kg twice weekly

- Administration
  - May be taken with or without food
Ethambutol

• Common side effects
  – Nausea/vomiting
  – Abdominal pain
  – Blurred vision
  – Rash
  – Peripheral neuropathy

• Serious adverse reactions
  – Optic neuritis
  – Blindness, irreversible

Images courtesy: http://pixshark.com/optic-neuritis-vs-normal.htm; http://swfhealthandwellness.com/treatment-people-suffer-peripheral-neuropathy-10/1

Ethambutol

• How supplied
  – Tablet, oral, as hydrochloride: 100 mg, 400 mg
  – Suspension available through compounding pharmacy

Images courtesy: www.epocrates.com and dailymed.nlm.nih.gov/dailymed
SECOND-LINE ANTI-TUBERCULOSIS MEDICATIONS

Cycloserine

- Dose
  - Adults: 10-15 mg/kg/day divided every 12 hours
  - Children: 10-15 mg/kg/day divided every 12 hours
  - Titrate dose as tolerated

- Administration
  - Take on an empty stomach
  - Supplement with pyridoxine
  - Avoid alcohol
Cycloserine

Dose titration should be completed within 2 weeks

- **Common side effects**
  - Behavioral changes
  - Headache
  - Skin changes
  - Dizziness

- **Serious adverse reactions**
  - Seizure
  - Depression
  - Psychosis
  - Suicidal ideation

Cycloserine

• How supplied
  – Capsule, oral: 250 mg

Ethionamide

• Dose
  – Adults: 15-20 mg/kg/day
    • 500-750 mg/day in single or divided dose
  – Children: 15-20 mg/kg/day divided in 2-3 doses
  – Titrate dose as tolerated

• Administration
  – Take with or after meals
  – Supplement with pyridoxine
  – Avoid alcohol
Ethionamide

- Common side effects
  - GI upset/anorexia
  - Metallic taste
  - Hypothyroidism
  - Acne
  - Hair loss
  - Gynecomastia
  - Menstrual irregularity

- Serious adverse reactions
  - Hepatotoxicity
Ethionamide

• How supplied
  – Oral, tablet: 250 mg

Levofloxacin

• Dose
  – Adult: 500-1000 mg/day
  – Children: 10 mg/kg/day for older children and 15-20 mg/kg/day divided bid for younger children

• Administration
  – Take 2 hours before or after aluminum, magnesium, or calcium-containing antacids, iron, vitamins, sucralfate, and/or milk-containing products
  – Promote adequate hydration
Levofloxacin

• Common side effects
  – Nausea and bloating
  – Headache
  – Dizziness
  – Insomnia
  – Arthralgias

• Serious adverse reactions
  – Tendon rupture (rare)
  – QT prolongation


Levofloxacin

• How supplied
  – Tablets, oral: 250 mg, 500 mg, 750 mg
  – Injection, solution: 25 mg/ml
  – Solution, oral: 25 mg/ml
  – Infusion, premixed with D5W: 250 mg, 500 mg, 750 mg

Images courtesy: www.epocrates.com
Moxifloxacin

• Dose
  – Adults: 400 mg daily
  – Children: No established dose

• Administration
  – Do not take milk-based products, antacid (especially aluminum-coating), vitamin supplements, or sucralfate within 2 hours of this medication

Moxifloxacin

• Common side effects
  – Nausea/diarrhea
  – Headache/dizziness
  – Arthralgias (< levofloxacin)

• Serious adverse reactions
  – Hepatotoxicity (rare)
  – Tendon rupture (rare)
  – QTc prolongation

Moxifloxacin

- How supplied
  - Tablets: 400 mg
  - Solution for IV: 400 mg/250 ml

Paser

- Dose
  - Adults: 8-12 grams per day divided 2-3 times daily
  - Children: 200-300 mg/kg/day divided 2-4 times daily

- Administration
  - Keep in the refrigerator
  - Take with or immediately following meals
  - Do not chew granules
  - Sprinkle on applesauce or yogurt; swirl in acidic juices
Paser

- Common side effects
  - GI upset
  - Hypothyroidism

- Serious adverse effects
  - Hepatotoxicity

Dose titration should be completed within 2 weeks

Paser

• How supplied
  – Oral, granules: 4 gram packet

Amikacin
Capreomycin
Streptomycin

• Dose
  – Adults
    • 15mg/kg/day, 5-7 days per week
    • 15-20 mg/kg/dose 2-3 days per week after initial dosing
      *after culture conversion*
  – Children
    • 15-30 mg/kg/day, 5-7 days per week
    • 15-30 mg/kg/day, 2-3 days per week after initial dosing

• Administration
  – Z-track method
Capreomycin

• Reconstitute 1 gram vial
  – 2 ml 0.9% Sodium Chloride Injection, or
  – 2 ml Sterile Water for Injection
    • May be stored up to 24 hours under refrigeration
• 2-3 minutes should be allowed for complete dissolution
• IV:
  – Reconstituted vial should be diluted in 100 ml of 0.9% Sodium Chloride Injection
  – Administer over 60 minutes

Capreomycin

• For administration of 1 gram dose, entire contents of vial should be given
• Smaller doses, follow chart below:

<table>
<thead>
<tr>
<th>Diluent Added to 1-g, 10 ml Vial</th>
<th>Volume of Capastat® Sulfate solution</th>
<th>Concentration (Approximate)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.15 ml</td>
<td>2.85 ml</td>
<td>370 mg/ml</td>
</tr>
<tr>
<td>2.63 ml</td>
<td>3.33 ml</td>
<td>315 mg/ml</td>
</tr>
<tr>
<td>3.3 ml</td>
<td>4 ml</td>
<td>260 mg/ml</td>
</tr>
<tr>
<td>4.3 ml</td>
<td>5 ml</td>
<td>210 mg/ml</td>
</tr>
</tbody>
</table>
Capreomycin

• Example
  – RJ comes into the clinic requiring 750 mg capreomycin IM. How many ml will you give IM if you reconstituted the vial with 2.15 ml?

370 mg x ? ml = 750 mg x 1ml

370 mg

? ml

? = 2.027 ml

Amikacin
Capreomycin
Streptomycin

• Common side effects
  – Local pain with IM injections
  – Electrolyte abnormalities
    • Hypocalcemia
    • Hypokalemia
    • Hypomagnesemia

• Serious adverse reactions
  – Nephrotoxicity
  – Vestibular toxicity/ototoxicity
Amikacin
Capreomycin
Streptomycin

• How supplied
  – Amikacin:
    • Injection, solution: 250 mg/ml (2ml, 4ml)
  – Capreomycin:
    • Injection, powder for reconstitution: 1 g
  – Streptomycin:
    • Injection, powder for reconstitution: 1 g

Linezolid

• Dose
  – Adults: 600 mg daily
  – Children: 10 mg/kg/dose every 8 hours

• Administration
  – May be taken with or without food
  – Supplement with pyridoxine
  – Avoid tyramine containing food/drinks
    • Aged cheeses, dried meats, sauerkraut, soy sauce, tap beers, red wines
  – Do not use with drugs that increase concentrations of serotonin in the body
Linezolid

• Common side effects
  – Diarrhea
  – Nausea
  – Optic and peripheral neuropathy

• Serious adverse reactions
  – Myelosuppression

Linezolid

• How supplied
  – Infusion, premixed: 200mg; 600mg
  – Powder for suspension, oral: 100mg/5ml
  – Oral, tablet: 600 mg
NEW AND INVESTIGATIONAL DRUGS

Bedaquiline (Sirturo®)
Clofazimine

Bedaquiline

• FDA indicated for multi-drug resistant pulmonary TB in adults ≥ 18 years old
  – Only used when effective treatment regimen cannot otherwise be provided
  – Not used for:
    • Latent TB
    • Drug-sensitive TB
    • Extra-pulmonary TB
• Should be used with at least 3 other susceptible drugs
Bedaquiline

• **Dose**
  – Adults
  • Weeks 1-2: 400 mg once daily, then
  • Weeks 3-24: 200 mg three times per week (with at least 48 hours between doses)

• **Administration**
  – Give with food
  – Swallow tablets whole with water
  – Avoid alcohol

Bedaquiline

• **Common side effects**
  – Nausea
  – Arthralgia
  – Headache
  – Elevated AST/ALT

• **Serious adverse reactions**
  – QT prolongation
  – Hepatotoxicity
  – Increase in mortality
Bedaquiline

- Restricted use in the United States
- How supplied
  - Oral, tablet: 100 mg

Clofazimine

- Dose
  - Adults: 100 to 200 mg daily
  - Children: limited data, but doses of 1 mg/kg/day have been given

- Administration
  - Take with food
Clofazimine

• Common side effects
  – Pink or red discoloration
    • Skin, conjunctiva, cornea and body fluids
  – GI upset
  – Rash/pruritis
  – Dry skin

• Serious adverse reactions
  – Gastrointestinal bleeding
  – Bowel obstruction

Clofazimine

• Not commercially available in the United States

• How supplied:
  – Oral, capsule: 50 mg
Drug-Drug Interactions

- CYP450 are the major enzymes involved in drug metabolism
- Most drugs undergo deactivation by CYPs (some activation)
- Many drugs may increase or decrease the activity of various CYP450 enzymes
  - Increase activity (inducers)
    - Rifampin
    - Rifabutin (< than rifampin)
### Drug Interactions

**CYP450 3A4**

- **Rifampin**
  - CYP inducer
  - Decrease levels of medications in blood
- **Rifabutin**
  - CYP substrate
- **Terbinafine**
  - Inactivated

#### Substrates (CYP3A)

<table>
<thead>
<tr>
<th>Substrates (CYP3A)</th>
<th>Inhibitors</th>
<th>Inducers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alprazolam/Clonazepam</td>
<td>Amiodarone</td>
<td>Carbamazepine</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>Cimetidine</td>
<td>Glucocorticoids</td>
</tr>
<tr>
<td>Buspirone</td>
<td>Clarithromycin</td>
<td>Phenobarbital</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>Erythromycin</td>
<td>Phenytoin</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Fluconazole</td>
<td>Primidone</td>
</tr>
<tr>
<td>Cilostazol</td>
<td>Fluoxetine</td>
<td></td>
</tr>
<tr>
<td>Citrate</td>
<td>Fluvoxamine</td>
<td></td>
</tr>
<tr>
<td>Citalopram</td>
<td>Grapefruit juice</td>
<td></td>
</tr>
<tr>
<td>Dapoxetine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Estrogens</td>
<td>Metronidazole</td>
<td></td>
</tr>
<tr>
<td>Protease inhibitors</td>
<td>Miconazole</td>
<td></td>
</tr>
<tr>
<td>Losartan</td>
<td>Nefazodone</td>
<td></td>
</tr>
<tr>
<td>Ondansetron</td>
<td>Nelfinavir</td>
<td></td>
</tr>
<tr>
<td>Prednisone</td>
<td>Ritonavir</td>
<td></td>
</tr>
<tr>
<td>Sertraline</td>
<td>Saquinavir</td>
<td></td>
</tr>
<tr>
<td>Simvastatin</td>
<td>Sertraline</td>
<td></td>
</tr>
<tr>
<td>Warfarin</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Rifampin will decrease levels of these meds in blood.

Decrease levels of rifabutin in blood.

Increase levels of rifabutin in blood.
Food-Drug Interactions

Best on empty stomach
- Rifampin
- Isoniazid
- Cycloserine
- Moxifloxacin
- Levofloxacin

Best with food
- Paser
- Clofazimine
- Ethionamide
- Bedaquiline

Avoid antacids
References

3. Micromedex® 2.0, Drugdex® Evaluations, Greenwood Village, CO: Truven Health Analytics, Inc. (Accessibility verified on September 15, 2014)