Pharmacology of Anti-Tuberculosis Drugs
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Chizoba Anozie, PharmD has the following disclosures to make:

- No conflict of interests
- No relevant financial relationships with any commercial companies pertaining to this educational activity
Pharmacology of Antituberculosis Drugs

Chizoba Anozie, PharmD
Objectives

- First-line anti-tuberculosis drugs
- Second-line anti-TB drugs
- Discuss Adverse reactions
- Review Drug Interactions
- Review New and Investigational drugs
Anti tuberculosis Drugs
First-Line Drugs

- Rifampin
- Rifabutin
- Isoniazid (INH)
- Pyrazinamide (PZA)
- Ethambutol
Rifampin

- **Class**: Rifamycin
- **Activity**: Bactericidal
- **Dose Adult**: 10mg/kg/dose (usually 600mg IV or PO)
- **Children**: 10 to 20mg/dose

**Administration:**
- Take without food
- May mix contents of capsule with applesauce or jelly
# Rifampin Adverse Effects

**Common**
- Reddish-orange body fluids
- Nausea, vomiting, diarrhea
- Rash, Pruritus
- Flu-like syndrome
- Elevated LFTs
- Vision changes

**Serious**
- Hepatitis
- Renal failure
- Hematological (thrombocytopenia, hemolytic anemia)
Rifabutin

**Class:** Rifamycin

**Activity:** Bactericidal

**Dose Adult:** 5mg/kg/dose (usually 300mg)

**Children:** Appropriate dose not known. Estimated at 5mg/kg/day

May be taken with or without food
## Rifabutin Adverse Effects

<table>
<thead>
<tr>
<th>Common</th>
<th>Serious</th>
</tr>
</thead>
<tbody>
<tr>
<td>o Reddish-orange body fluids</td>
<td>o Hepatotoxicity</td>
</tr>
<tr>
<td>o Rashes, skin discoloration (bronzing or pseudojaundice)</td>
<td>o Leukopenia, Neutropenia, thrombocytopenia</td>
</tr>
<tr>
<td>o Arthralgia</td>
<td>o Anterior uveitis and other eye toxicities</td>
</tr>
<tr>
<td>o Taste changes</td>
<td></td>
</tr>
</tbody>
</table>
Isoniazid (INH)

- **Class:** Isonicotinic acid hydrazide
- **Activity:** Bactericidal
- **Dose (Adult):** 5mg/kg/day (PO or IV) (usual dose 300mg daily)
- **Administration:** Best absorbed on empty stomach (about 50% reduction with fatty meal)
- **Avoid Alcohol**
## Isoniazid (INH) Adverse Effects

### Common
- Paresthesia
- Pyridoxine deficiency
- Epigastric discomfort
- Cramping with oral solution
- Elevated LFTs

### Serious
- Hepatotoxicity
- Hypersensitivity reactions
- Drug-induced lupus
- CNS changes
- Peripheral neuropathy
Pyrazinamide (PZA)

- **Class**: Synthetic derivative of nicotinamide
- **Activity**: Bactericidal
- **Dose (Adult)**: 25mg/kg/day (max 2gm)
- May be taken with or without food

![Pyrazinamide Tablets B.P.](image)
Pyrazinamide (PZA)  
Adverse Effects

<table>
<thead>
<tr>
<th>Common</th>
<th>Serious</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gout (hyperuricemia)</td>
<td>Hepatotoxicity</td>
</tr>
<tr>
<td>Elevated LFTs</td>
<td>Anemia</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>Drug-induced myopathy</td>
</tr>
<tr>
<td>Rash</td>
<td></td>
</tr>
<tr>
<td>GI symptoms</td>
<td></td>
</tr>
<tr>
<td>Photosensitivity</td>
<td></td>
</tr>
</tbody>
</table>
Ethambutol

Class: Unspecified
Activity: Bacteriostatic
Dose (Adult):
15-25mg/kg/day
Administration:
- May be taken with or without food
- Avoid aluminum containing antacid within 4hrs of admin.
Ethambutol
Adverse Effects

Common
- Nausea, vomiting
- Abdominal discomfort
- Blurred vision
- Rash
- Psychiatric symptoms (mania, hallucinations, psychosis)

Serious
- Optic neuritis
- Peripheral neuropathy
- Blindness (irreversible)
Second-Line Drugs

- Levofloxacin
- Moxifloxacin
- Cycloserine
- Ethionamide
- Para-aminosalicylic acid (Paser)
- Amikacin
- Streptomycin
- Capreomycin
- Linezolid
Levofloxacin (Levaquin)

- **Class**: Fluoroquinolone
- **Activity**: Bactericidal
- **Dose (Adult)**: 500mg – 1000mg daily
Levofloxacain

Administration:

Do not administer within 2 hrs of ingestion of milk-based products, antacids or drugs containing divalent cations (iron, aluminum, magnesium, calcium, zinc, vitamins, sucralfate, didanosine).
## Levofloxacin Adverse Effects

<table>
<thead>
<tr>
<th>Common</th>
<th>Serious</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Nausea and bloating</td>
<td>- Tendon rupture (rare)</td>
</tr>
<tr>
<td>- Headache</td>
<td>- QT prolongation</td>
</tr>
<tr>
<td>- Dizziness</td>
<td>- Peripheral neuropathy</td>
</tr>
<tr>
<td>- Arthralgia</td>
<td></td>
</tr>
<tr>
<td>- Tendinitis</td>
<td></td>
</tr>
<tr>
<td>- Photosensitivity</td>
<td></td>
</tr>
</tbody>
</table>

*Diagram showing an ECG tracing*
Moxifloxacin (Avelox)

- **Class:** Fluoroquinolone
- **Activity:** Bactericidal
- **Dose (Adult):** 400mg/day
- **Administration:**
  - Do not administer within 2 hrs of ingestion of milk-based products, antacids or drugs containing divalent cations (iron, aluminum, magnesium, calcium, zinc, vitamins, sucralfate, didanosine).
### Moxifloxacin Adverse Effects

#### Common
- Nausea, diarrhea
- Headache, dizziness
- Arthralgia
- Tendinitis

#### Serious
- Hepatotoxicity (rare)
- Tendon rupture (rare)
- QT prolongation
- Peripheral neuropathy
Cycloserine (Seromycin)

- **Class:** Analog of D-alanine
- **Activity:** Bacteriostatic

- **Dose (Adult):** 15 – 20mg/kg/day (usually 250 – 500mg once or BID)
- **Children:** 15 – 20mg/kg/day in 1 to 2 divided doses

- **Administration:**
  - Take on empty stomach
  - Give Vitamin B6 supplement
## Cycloserine Adverse Effects

<table>
<thead>
<tr>
<th>Common</th>
<th>Serious</th>
</tr>
</thead>
<tbody>
<tr>
<td>- CNS toxicity (behavioral changes, headache, dizziness, lethargy)</td>
<td>- Seizure</td>
</tr>
<tr>
<td>- Peripheral neuropathy</td>
<td>- Depression</td>
</tr>
<tr>
<td>- Skin changes</td>
<td>- Psychosis</td>
</tr>
<tr>
<td>- Skin rash (lichenoid eruptions)</td>
<td>- Suicidal ideation</td>
</tr>
<tr>
<td></td>
<td>- Steven-Johnson syndrome</td>
</tr>
</tbody>
</table>
Ethionamide (Trecator)

- Derivative of Isonicotinic acid
- Bactericidal

**Dose:**

- **Adult:** 15 – 20mg/kg/day (usually 250 – 500mg once or BID)
- **Children:** 15 – 20mg/kg/day in 1 to 2 divided doses
Ethionamide Adverse Effects

Common
- GI upset, anorexia
- Metallic taste
- Endocrine effects (Gynecomastia, hair loss, acne, impotence, menstrual irregularity, reversible hypothyroidism)

Serious
- Hepatotoxicity
- Neurotoxicity
- Optic neuritis

Image courtesy: healthline.com
Para-aminosalicylic acid (Paser)

- **Class**: Salicylic acid; anti-folate
- **Activity**: Bacteriostatic

**Dose:**

**Adult**: 8 – 12 grams/day (usually 4 grams 2 – 3 x daily)

- **Administration**:
  - Take with food
  - Store in refrigerator
  - May sprinkle on applesauce or yogurt
## Para-aminosalicylic acid (Paser) Adverse Effects

<table>
<thead>
<tr>
<th>Common</th>
<th>Serious</th>
</tr>
</thead>
<tbody>
<tr>
<td>- GI symptoms (titrate dose over 2 weeks)</td>
<td>- Hepatotoxicity (rare)</td>
</tr>
<tr>
<td>- Hypothyroidism (reversible)</td>
<td>- Coagulopathy (rare)</td>
</tr>
</tbody>
</table>
Amikacin/Streptomycin/Capreomycin

- **Amikacin, Streptomycin**
  - **Class:** Aminoglycoside

- **Capreomycin**
  - **Class:** Cyclic polypeptide

**Activity:** Bactericidal
Amikacin/Streptomycin/Capreomycin

Dose:
- Adult: 15mg/kg/day
- Children: 15 – 20mg/kg/day
- Administration: IM or IV
Amikacin/Capreomycin/Streptomycin Adverse Effects

Common
- Local pain with IM injections
- Electrolyte abnormalities (hypokalemia, hypocalcemia, hypomagnesemia)

Serious
- Nephrotoxicity
- Ototoxicity
- Vestibular toxicity
**Linezolid (Zyvox)**

- **Class:** Oxazolidinones
- **Activity:** Bactericidal
- **Dose (Adult):** 600mg/day
- **Children:** 10mg/kg/dose

**Administration:**
- Take with or without food
- Take Vitamin B6 supplement
- Avoid tyramine containing food (aged cheese, dried meat, soy sauce, sauerkraut, red wine, tap beer; avoid drug that increase serotonin conc.)
## Linezolid Adverse Effects

<table>
<thead>
<tr>
<th>Common</th>
<th>Serious</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>Myelosuppression</td>
</tr>
<tr>
<td>Nausea</td>
<td>Lactic acidosis</td>
</tr>
<tr>
<td>Headache</td>
<td>Peripheral neuropathy</td>
</tr>
<tr>
<td></td>
<td>Optic neuritis</td>
</tr>
<tr>
<td></td>
<td>Serotonin syndrome</td>
</tr>
</tbody>
</table>

Images: courtesy of unitedintegratedhealth.com
New and Investigational Drugs

- Clofazimine
  - Investigational Drug - FDA
- Bedaquiline
  - Restricted use in the US
- Delamanid
  - Conditional approval by European medicines agency (EMA)
  - Not yet approved by FDA
Clofazimine (Lamprene)
Investigational Drug

- Not commercially available in the US.
- Available from FDA via single-patient INDs for TB

Adult Dose:
100 – 200mg/day

Administration:
- PO only
- Take with food
## Clofazimine Adverse Effects

### Common
- Pink or red discoloration of skin, conjunctiva, cornea, and body fluids
- GI intolerance
- Photosensitivity
- Dry skin, rash, pruritus

### Serious
- GI bleeding
- Bowel obstruction
- Retinopathy
Bedaquiline (Sirturo)

- Restricted use in the US
- FDA indicated for multi-drug resistant pulmonary TB in adults 18 yrs old and older
- Use only when other treatment options cannot be utilized

**Do not use for**
- Latent TB
- Extra-pulmonary TB
- Drug sensitive TB

Use with at least 3 other susceptible drugs
Bedaquiline

**Dosing:**
- Weeks 1 – 2: 400mg daily then,
- Weeks 3 – 24: 200mg 3 times per week (at least 48 hrs between doses)

**Administration:**
- Take with food
- Swallow whole tablet with water
- Avoid alcohol
Bedaquiline Adverse Effects

Common
- Nausea
- Arthralgia
- Headache
- Elevated AST/ALT

Serious
- QT prolongation
- Hepatotoxicity
- Increase mortality

Image courtesy: https://medicalguidelines.msf.org/viewport/TUB/files/
Drug-drug Interactions

Drug-Drug Interaction

- Drug
- Drug(s)

Possible Effects:
- Decrease Action of Drug(s)
- Increase Action of Drug(s)
- Cause Adverse Effects

images courtesy: aidsinfo.nih.gov
Drug-drug Interactions

- Most clinically relevant drug-drug interactions involve Rifamycins (Rifampin > Rifabutin)
- Rifamycins are inducers of several metabolic pathways especially involving various isoenzymes of the cytochrome P450 (CYP) system
- Rifamycins can decrease serum concentrations of many drugs (e.g., most of HIV – 1 protease inhibitors) to sub therapeutic levels
Drug-drug Interactions
Rifamycins

<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>Rifampin</td>
</tr>
<tr>
<td>Citalopram</td>
<td>Fluvoxamine</td>
<td></td>
</tr>
<tr>
<td>Clindamycin</td>
<td>Grapefruit juice</td>
<td></td>
</tr>
<tr>
<td>Clindamycin</td>
<td>Indinavir</td>
<td></td>
</tr>
<tr>
<td>Dapsone</td>
<td>Itraconazole</td>
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</tr>
<tr>
<td>Estrogens</td>
<td>Ketoconazole</td>
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</tr>
<tr>
<td>Protease inhibitors</td>
<td>Metronidazole</td>
<td></td>
</tr>
<tr>
<td>Losartan</td>
<td>Miconazole</td>
<td></td>
</tr>
<tr>
<td>Ondansetron</td>
<td>Nefazodone</td>
<td></td>
</tr>
<tr>
<td>Prednisone</td>
<td>Nelfinavir</td>
<td></td>
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<tr>
<td>Sertraline</td>
<td>Ritonavir</td>
<td></td>
</tr>
<tr>
<td>Simvastatin</td>
<td>Saquinavir</td>
<td></td>
</tr>
<tr>
<td>Warfarin</td>
<td>Sertraline</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
Drug-drug Interactions
Isoniazid

- Potent inhibitor of several CYP450 isoenzymes
- Increases concentration of some drugs to point of toxicity
  - Phenytoin
  - Carbamazepine
  - Diazepam
  - Triazolam
Food-drug Interactions

Best on Empty Stomach
- Rifampin
- Isoniazid
- Cycloserine
- Moxifloxacin
- Levofloxacin

Best with food
- Paser
- Clofazimine
- Ethionamide
- Bedaquiline
Questions
Glossary of Terms

- **Bactericidal** - Capable of killing bacteria outright
- **Bacteriostatic** - Capable of inhibiting the growth or reproduction of bacteria
- **DOT** – Directly observed therapy
- **Paresthesia** - A burning or prickling sensation that is usually felt in the hands, arms, legs, or feet, but can also occur in other parts of the body.
- **Serotonin syndrome** - A group of symptoms that may occur following use of certain serotonergic medications or drugs. Symptoms include; high body temperature, agitation, increased reflexes, tremor, sweating, dilated pupils, and diarrhea.
- **IND** – Investigational New Drug
References


2. Micormedex 2.0, Drugdex Evaluations, Greenwood Village, CO: Truven Health Analytics, Inc.
