Adverse Drug Reactions of TB Medications

Dean Tsukayama
Medical Director
Hennepin County Public Health Clinic
Objectives

• Recognize the common side effects of first line tuberculosis medication

• Know the risk factors, associated drugs, and management of hepatotoxicity.

• Be familiar with the side effects of second-line tuberculosis medication
How should I manage this adverse drug reaction?

Chance favors the prepared mind
Louis Pasteur
Anticipating Adverse Effects

- Universal Adverse Effects
- Common AE of first-line drugs
- Important AE of second-line drugs
- Baseline and follow-up monitoring
### Adverse Effects of First-line Drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Adverse Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>isoniazid</td>
<td>hepatotoxicity, peripheral neuropathy, CNS effects, lupus-like syndrome, monoamine poisoning</td>
</tr>
<tr>
<td>rifampin</td>
<td>flu-like syndrome, hepatotoxicity, anemia, thrombocytopenia, renal failure, drug interactions</td>
</tr>
<tr>
<td>pyrazinamide</td>
<td>hepatotoxicity, polyarthralgia, gout</td>
</tr>
<tr>
<td>ethambutol</td>
<td>impaired vision, peripheral neuropathy</td>
</tr>
</tbody>
</table>
## Adverse Effects of Second-line Drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Adverse Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>aminoglycoside</td>
<td>ototoxicity, nephrotoxicity,</td>
</tr>
<tr>
<td>cycloserine</td>
<td>neuropsychiatric toxicity, peripheral neuropathy</td>
</tr>
<tr>
<td>ethionamide</td>
<td>hepatotoxicity, neurotoxicity, hypothyroidism</td>
</tr>
<tr>
<td>fluoroquinolone</td>
<td>neurotoxicity, tendinitis, hepatotoxicity</td>
</tr>
<tr>
<td>PAS</td>
<td>hepatotoxicity, GI distress, hypothyroidism, coagulopathy</td>
</tr>
</tbody>
</table>
## Monitoring for Adverse Effects

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td>Liver function panel, creatinine, CBC, platelets, visual acuity and color vision</td>
</tr>
<tr>
<td><strong>Follow-up</strong></td>
<td>eye exam if on ethambutol, ALT if at risk for hepatotoxicity</td>
</tr>
</tbody>
</table>
Top Ten Troubles

1. Gastrointestinal upset
2. Rash/pruritus
3. Peripheral neuropathy
4. Hepatotoxicity
5. Hematologic toxicity
6. PZA and gout
7. Ethambutol and vision
8. Hypothyroidism
9. CNS toxicity
10. Drug interactions
Tools for management

- Consider a non-TB drug or condition
- Treat symptoms and continue the medication
- Modify drug delivery
- Stop the drug(s) and follow clinically
- Re-challenge after symptoms abate
- Use different drug(s)
- Measure drug levels
- Hospitalize during medication re-challenge
Toolbox

• Use different drug(s)
• Measure drug levels
• Hospitalize for close monitoring during medication re-challenge
## Gastrointestinal Upset

<table>
<thead>
<tr>
<th>Problem</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastric discomfort</td>
<td>Give medication with food</td>
</tr>
<tr>
<td></td>
<td>Change time of administration</td>
</tr>
<tr>
<td></td>
<td>Acid suppression</td>
</tr>
<tr>
<td></td>
<td>Check for H. pylori</td>
</tr>
<tr>
<td></td>
<td>Discontinue drugs and follow response</td>
</tr>
<tr>
<td>Nausea</td>
<td>Discontinue drugs and follow response</td>
</tr>
<tr>
<td></td>
<td>Check for hepatitis</td>
</tr>
<tr>
<td></td>
<td>Anti-emetics</td>
</tr>
<tr>
<td>Aversion to pills</td>
<td>Crush pills</td>
</tr>
<tr>
<td></td>
<td>Liquid form of medication</td>
</tr>
<tr>
<td></td>
<td>Split the dose</td>
</tr>
</tbody>
</table>
Rash/Pruritus

- Check other drugs or topical preparations
- Early onset, urticaria could mean more serious allergic reaction
- Extensive rash - stop medication, check for other affected systems
- Petechiae - check platelets, suspect rifampin
- Symptomatic treatment with antihistamines
- Re-challenge
  - can start low and work up to therapeutic dose of drug
  - can start with one drug, then add successive drugs every 3-4 days if there is no reaction to the preceding drug. Order of drugs not established, I usually start with rifampin.
Peripheral Neuropathy

- Check for neuropathy before starting TB medication
- Isoniazid is the usual culprit, but quinolones, ethambutol, cycloserine and linezolid have been implicated
- Tuberculosis itself can present with neuropathy
- Treat with increasing dose of pyridoxine to a maximum of 200 mg daily
- If no improvement after treatment, consider discontinuation of isoniazid
Hepatotoxicity

• Risk factors for injury
• Risk in pregnancy
• Liver enzyme elevation
• Drugs associated w/ liver injury
• Confirming the drug causing injury
• Check for hematologic, renal injury
• Other causes of hepatitis
• Liver-sparing treatment regimen
Hepatotoxicity

- Risk factors for injury
- Risk in pregnancy
- Liver enzyme elevation
- Drugs associated with liver injury
- Confirming the drug causing injury
- Check for hematologic, renal injury
- Other causes of hepatitis
- Liver-sparing treatment regimen

- Alcohol consumption
- Other hepatotoxic drugs
- Previous elevation of ALT
- Combination TB drugs
- Elderly
- Asian male
Hepatotoxicity

- Risk factors for injury
- Risk in pregnancy
- Liver enzyme elevation
- Drugs associated w/ liver injury
- Confirming the drug causing injury
- Check for hematologic, renal injury
- Other causes of hepatitis
- Liver-sparing treatment regimen

- May have higher rate of INH-induced hepatitis in pregnancy and within 3 months post-partum
- Defer LTBI treatment in low-risk patients until after pregnancy

Hepatotoxicity

- Risk factors for injury
- Risk in pregnancy
- Liver enzyme elevation
- Drugs associated with liver injury
- Confirming the drug causing injury
- Check for hematologic, renal injury
- Other causes of hepatitis
- Liver-sparing treatment regimen

- ALT more specific for liver than AST
- Bilirubin more associated with rifampin
- Evaluate for severity of disease (marked enzyme rise, jaundice, coagulopathy, hypoglycemia)
- Stop drug when:
  - x5 elevation in asymptomatic patient
  - x3 elevation in symptomatic patient
Hepatotoxicity

- Risk factors for injury
- Risk in pregnancy
- Liver enzyme elevation
- Drugs associated w/ liver injury
- Confirming the drug causing injury
- Check for hematologic, renal injury
- Other causes of hepatitis
- Liver-sparing treatment regimen

- isoniazid
- rifampin
- pyrazinamide
- ethionamide
- para-aminosalicylic acid
- fluoroquinolones
Hepatotoxicity

- Risk factors for injury
- Risk in pregnancy
- Liver enzyme elevation
- Drugs associated w/ liver injury
- Confirming the drug causing injury
- Check for hematologic, renal injury
- Other causes of hepatitis
- Liver-sparing treatment regimen

Rechallenge with the suspected offending agent with more than twofold serum alanine aminotransferase (ALT) elevation, and discontinuation leading to a fall in ALT, is the strongest confirmation of the diagnosis.

Hepatotoxicity

- Risk factors for injury
- Risk in pregnancy
- Liver enzyme elevation
- Drugs associated w/ liver injury
- Confirming the drug causing injury
- Check for hematologic, renal injury
- Other causes of hepatitis
- Liver-sparing treatment regimen

- Hematologic
  - Anemia
  - Leukopenia
  - Thrombocytopenia
  - Eosinophilia

- Renal
  - BUN and creatinine
  - urine eosinophils
Hepatotoxicity

- Risk factors for injury
- Risk in pregnancy
- Liver enzyme elevation
- Drugs associated w/ liver injury
- Confirming the drug causing injury
- Check for hematologic, renal injury
- Other causes of hepatitis
- Liver-sparing treatment regimen

- Check for viral hepatitis (A, B, C)
- Consider alcoholic hepatitis
- Consider autoimmune hepatitis
- May need consult and liver biopsy
Hepatotoxicity

- Risk factors for injury
- Risk in pregnancy
- Liver enzyme elevation
- Drugs associated w/ liver injury
- Confirming the drug causing injury
- Check for hematologic, renal injury
- Other causes of hepatitis
- Liver-sparing treatment regimen

- ethambutol
- quinolone
- aminoglycoside
- cycloserine
CNS Toxicity

- quinolone
  - anxiety, headache, confusion,
- isoniazid
  - seizure
  - depression
- cycloserine
  - psychosis
## CNS Toxicity

<table>
<thead>
<tr>
<th>Problem</th>
<th>Drug</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>anxiety</td>
<td>quinolone, isoniazid, cycloserine</td>
<td>observation</td>
</tr>
<tr>
<td>seizure</td>
<td>isoniazid, cycloserine</td>
<td>monitor drug levels of anti-seizure medication</td>
</tr>
<tr>
<td>depression</td>
<td>cycloserine</td>
<td>prevention with high dose pyridoxine, may need anti-depressant</td>
</tr>
<tr>
<td>psychosis</td>
<td>cycloserine</td>
<td>measure drug level, decrease dose, stop medication, Psychiatry consultation</td>
</tr>
</tbody>
</table>
Hematologic Toxicity

- Rifampin most frequently implicated but toxicity can occur with all first-line drugs
- “flu-like syndrome” with rifampin can result in depression of anemia, leukopenia, and thrombocytopenia
- Hematology consultation can be helpful
- G-CSF has been used for neutropenia
# Pyrazinamide and Gout

<table>
<thead>
<tr>
<th>Problem</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>arthralgia</td>
<td>NSAIDS if needed</td>
</tr>
<tr>
<td>uric acid elevation</td>
<td>nothing if asymptomatic</td>
</tr>
<tr>
<td>flare of gout</td>
<td>stop PZA if possible, try to lower uric acid levels</td>
</tr>
<tr>
<td>persistent arthritis</td>
<td>look for another cause of inflammation</td>
</tr>
</tbody>
</table>

Isoniazid can lead to joint inflammation as a manifestation of SLE syndrome.
Ethambutol and Vision

- Check visual acuity and color discrimination at baseline.
  - Higher risk with renal failure or dose greater than 15 mg/kg.
  - Dosing should be 15 mg/kg for prolonged course (more than 2 months).
  - If visual disturbance suspected, discontinue drug immediately and refer for Ophthalmology evaluation.
  - May lead to severe vision loss if ethambutol not stopped.
Hypothyroidism

- Seen with ethionamide and PAS
- Check TSH at baseline and monitor
- May need thyroid replacement
<table>
<thead>
<tr>
<th>Drug</th>
<th>Interacting Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>isoniazid</td>
<td>anti-seizure medication, coumadin</td>
</tr>
<tr>
<td>rifampin</td>
<td>Multiple drugs, notably HIV medication, immunomudulators, coumadin</td>
</tr>
<tr>
<td>quinolone</td>
<td>drugs causing QT prolongation</td>
</tr>
<tr>
<td>pyrazinamide</td>
<td>cyclosporine</td>
</tr>
</tbody>
</table>
Final Thoughts

• For non-serious adverse effects, can continue to treat, adding measures to treat symptoms

• For serious adverse effects, stopping all the TB drugs is a reasonable step

• Consider the seriousness of the reaction in deciding whether re-challenge is possible

• For re-challenge, starting drugs one at a time can identify the culprit drug

• Rifabutin can sometimes be substituted for rifampin