Tb Medications and Adverse Effects

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Dorland’s Medical Dictionary says:

- **Side effect** – a consequence other than the one(s) for which an agent or measure is used, as the adverse effects produced by a drug, especially on a tissue or organ system other than the one sought to be benefited by its administration.

- **Adverse reaction** – unexpected, serious symptoms coinciding with the administration of a drug; see also “side effect”

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**Adverse Drug Reaction Defined**

“**Official**”

“Unintended, undesirable, and unexpected effects of prescribed medications or of medication errors that require discontinuing a medication or modifying the dose, require initial or prolonged hospitalization, result in disability, require treatment with a prescription medication, result in cognitive deterioration or impairment, are life threatening, result in death or result in congenital anomalies”

**JCAHO**
### Adverse Drug Events Defined
#### “Unofficial”

<table>
<thead>
<tr>
<th>Side effects</th>
<th>Side effects</th>
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<tbody>
<tr>
<td>Unpleasant, but mild reactions</td>
<td>Gas</td>
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<td>No long lasting health effects</td>
<td>Bloating</td>
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<td>Do not usually require changes in therapy</td>
<td>Mild nausea</td>
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<td>Discoloration of body fluids</td>
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<td>Irritability</td>
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<td>Difficulty sleeping</td>
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<td>Photosensitivity</td>
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<tr>
<td>Drug toxicity</td>
<td>Drug toxicity</td>
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<tr>
<td>More serious</td>
<td>Significant GI disturbances</td>
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<td>May be life threatening</td>
<td>Hepatotoxicity</td>
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<td>Require modifying the dose or discontinuation of drug</td>
<td>Dermatologic and hypersensitivity reactions</td>
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<td>May require additional therapy and/or hospitalization</td>
<td>Ophthalmic toxicity</td>
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<td></td>
<td>CNS toxicity</td>
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<td>Neurotoxicity</td>
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<td>Ototoxicity</td>
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<td>Musculoskeletal adverse effects</td>
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<td>Renal toxicity</td>
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</table>
First Line Drugs

- Isoniazid ~ early 50’s
- Rifampin ~ late 60’s
- Rifapentine
- Rifabutin ~ 1995
- Ethambutal
- Pyrazinamide (PZA)

Second Line Drugs

- Cycloserine
- Clofazimine ~ last resort usually
- Ethionamide
- Levofloxacin, Moxifloxacin, and Gatifloxacin (not avail. In US)
- P-Aminosalicylic acid (PAS) ~1944
- Streptomycin ~ 1944 (PAS and Strep were the first 2 TB drugs used)
- Amikacin/Kanamycin
- Capreomycin
- Augmentin
- Linezolid
Isoniazid

- Bacterialcidal
- Spectrum – Mtb mainly
- Adverse Drug Reaction (ADR) and Side Effects (SE)
  - hepatotoxicity
  - peripheral neuropathy (alcoholics and diabetics)
  - GI upset, headaches
  - rash

Uncommon SE at conventional dosing: hemolytic anemia, convulsions, dizziness, ataxia and psychosis
- cytochrome P-450 inhibitor

- Monitoring – liver functions mainly

INH continued:

- weak inhibitor of monoamine oxidase in plasma – avoid tyramine containing foods such as cheeses, wines, pickled meats, sauerkraut, tuna fish (could cause flushing, warmth, nasal stuffiness, mild tachycardia and systolic HTN)
- Tyramine – is metabolized by monoamine oxidase and causes the release of dopamine, epinephrine and norepinephrine
- There have been some articles expressing concern about the combination of SSRI’s and INH, because INH is a weak inhibitor of MAO in plasma. (Selective serotonin reuptake inhibitors and isoniazid: Evidence of a potential adverse reaction, Military Medicine, Dec 2001, Michael Doyle. Treatment of Comorbid Tuberculosis and Depression, Primary Care Companion, J Clinical Psychiatry 2001;3(6).)
- Monoamine oxidase inhibitors (MAOI’s) are a potentially dangerous drug that have been and are rarely used for the treatment of depression anymore due to the development of SSRI’s which are relatively safe.
- MAOI’s and SSRI’s are contraindicated due to the possibility of developing Serotonin Syndrome (excitation, diaphoresis, myoclonus, hyperthermia, rigidity, and Htn.)
Baseline Laboratory Monitoring
LTBI - INH

- Baseline LFT’s (ALT*, bilirubin) are not necessary except for patients with the following risk factors
  - HIV infection treated with HAART
  - History of chronic liver disease (hepatitis B/C, alcoholic hepatitis, cirrhosis)
  - Previous abnormal ALT and/or bilirubin
  - Regular use of alcohol
  - Pregnancy or early postpartum period (within 3 months of delivery)
  - Other: consider individually, e.g., “healthy individuals” > 35 yrs., patients taking other hepatotoxic drugs

*ALT: more specific for liver injury

Periodic Laboratory Monitoring
LTBI - INH

- Repeat laboratory monitoring if patient has
  - Abnormal baseline results (> 3 X ULN)
    - Repeat ALT, bilirubin
    - Screen for possible causes (viral, alcohol, hepatotoxic drugs)
    - Carefully weigh risks of treatment in setting of ALT elevation, chronic alcohol consumption, severe liver disease manifested by low albumin and coagulopathy or encephalopathy
      - Consider more frequent monitoring (q 2 – 4 wks. for first 2 – 3 mo.), if treated
      - Discontinue treatment if > 2 – 3 X increase above baseline, jaundice, or significant increase in bilirubin
    - High risk for adverse reactions (see indications for baseline screening)
Periodic Laboratory Monitoring
LTBI - INH

– Symptoms of adverse reaction
  • Hold medications until results of LFT’s obtained
– Liver enlargement or tenderness during examination

Periodic Laboratory Monitoring
LTBI - INH

• Asymptomatic increase in LFT’s occurs in 10-20% of persons taking INH
  • LFT’s usually return to normal without interruption of therapy
• Hold treatment if
  – Transaminase levels (ALT) > 3X upper limit of normal and patient has symptoms of hepatotoxicity
  – Transaminase levels (ALT) > 5X upper limit of normal and patient is asymptomatic
• More frequent monitoring (q 2 wks.) if rapid rise in ALT
**Rifampin**

- Bacterialcidal
- Spectrum – Mtb, staph, meningococcus, several others
- ADR
  - GI
  - rash
  - arthralgias, myalgias
  - hepatic – LFT’s, hyperbilirubinemia – competes with bilirubin for excretory pathways in the liver at the cellular level
  - thrombocytopenia – if dosing above 600mg/d risk increases
  - **pancreatitis**
  - cytochrome P-450 inducer – lots of significant drug interactions, decreases levels of oral anticoagulants, benzo’s, oral contraceptives, theophyllin, phenytoin, methadone, thyroid hormone, HIV meds (some PI’s and NNRTI’s), Ca channel blockers, beta blockers, etc..

**Rifabutin**

- Cross resistance with rifampin
- Less LFT effect than rifampin
- Less potent cytochrome inducer than rifampin ~ 40%
- ADR
  - uveitis
  - neutropenia – dose related
  - hepatitis
  - rash
PZA - pyrazinamide

- Bacterialcidal
- ADR
  - rash
  - elevates uric acid – usually asymptomatic, but can precipitate acute gouty arthritis attacks
  - hepatotoxicity – usually with higher doses, PZA causes problems with the liver less frequently than INH, but when it does, it can be more severe and prolonged
  - arthralgias
  - can affect the management of diabetes patients
- Lab – LFT’s, uric acid levels, renal function

Ethambutal

- Bacteriostatic/cidal in higher doses
  - primarily used to prevent emergence of resistant organisms
- Spectrum – Mtb, MOTT, MAC
- ADR –
  - optic neuritis (retrobulbar) – which affects visual acuities and red/green color vision
  - can affect one or both eyes
  - effect is dose related
  - baseline testing – visual acuities (Snellen) and Ishihara charts to check for color discrimination. Toxicity is reversible if caught early and meds stopped.
  - Blindness can occur
  - rash, increased uric acid levels (not as bad as PZA)
Baseline Laboratory Monitoring
TB Disease

• All adults
  – AST, ALT, bilirubin, alkaline phosphatase, serum creatinine, CBC with platelet count
  – HIV
    • CD-4 lymphocyte count, if HIV-infected
• Screen for viral hepatitis in at risk patients
• Amikacin: serum creatinine

Periodic Laboratory Monitoring
TB Disease

• Unnecessary if treated with first-line drugs unless
  – Baseline lab abnormalities
  – Chronic alcohol consumption
  – Other hepatotoxic drugs
  – Viral hepatitis or history of liver disease
  – HIV infection
  – Prior DILI (drug induced liver injury)
  – Clinical reasons to obtain lab measurements
**Overview**

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<th>DRUGS*</th>
<th>TOXICITIES</th>
<th>INFORMATION</th>
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<td>INH</td>
<td>GI Disturbances</td>
<td>Drugs Involved</td>
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<tr>
<td>Rifampin/Rifabutin</td>
<td>Drug-Induced Hepatitis</td>
<td>Monitoring</td>
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<td>PZA</td>
<td>Immune Reactions</td>
<td>Assessment</td>
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<td>EMB</td>
<td>Ophthalmic Toxicity</td>
<td>Response</td>
</tr>
<tr>
<td>(Fluoroquinolones: LV, MX, GT)</td>
<td>CNS/Neurotoxicity</td>
<td></td>
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<tr>
<td>(Aminoglycosides: AK, KN, SM)</td>
<td>Ototoxicity</td>
<td></td>
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<tr>
<td>*Treatment of TB Disease</td>
<td>Musculoskeletal</td>
<td></td>
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<tr>
<td></td>
<td>Renal Toxicity</td>
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**ESRD/Dialysis patients**

- Usually give meds 3X a week after dialysis to prevent meds from being dialyzed and to facilitate DOT.
- INH and RIF is metabolized by the liver and could be given daily but usually given 3X a week
- PZA, EMB, fluoroquinolones, strep (and other injectibles) need to be adjusted to 3X per week due to there metabolism by the kidneys.
Hepatitis and HIV

- HIV - Rifampin causes decreases in certain HIV meds (protease inhibitors and NNRTI’s), usually use Rifabutin.
- HCV – PZA is not used, will try and use Rifampin for PT vs. INH due to less hepatotoxicity.
- If Class 3 – will utilize controlled toxicity and change drugs if patient becomes symptomatic or if liver functions are > 5X the upper limits of normal.

Hepatitis, clinical signs

- Early – fatigue, rash, poor appetite, nausea, bloating
- Late – vomiting, abdominal pain, jaundice, dark urine, light stools, neurological problems
- Lab eval. – AST/ALT, bilirubin, clotting studies (evaluates extent of inflammation and liver function)
General rules of thumb for hepatotoxicity

- Hold meds if LFT’s > 3x normal and pt is symptomatic
- Hold meds if LFT’s > 5x normal in the absence of symptoms
- Hold meds if T. bili is increased > 2x normal with no other poss. explanation

Pregnancy

- Untreated TB represents a far greater risk to the pregnant patient than does treatment of the disease
- Isoniazid, rifampin, ethambutal and PZA
- PZA used in UK and WHO regions without adverse fetal consequences
- Insufficient data in US for routine PZA use.
- Aminoglycosides should not be used due to effects on ear development and risk of congenital deafness
- PAS was used in the past with INH w/o consequence
- Other drugs, fluoroquinolones, cycloserine, ethionamide, not enough data
Drug Interactions

• INH and RIF
• Cytochrome p450 isoenzymes
• INH is a cytochrome inhibitor
• RIF is a cytochrome inducer
• Isoniazid may increase the plasma concentrations of certain drugs by inhibiting their elimination, such as:
  • phenytoin, carbamazepine, valproic acid
  • warfarin, theophyllin, to name a few.

Drug Interactions cont.

• Rifampin (rifamycins) may decrease the plasma concentrations of many drugs by speeding up their elimination, such as:
  • phenytoin, carbamazepine, valproic acid
  • warfarin, theophyllin, digoxin, certain HIV meds.
• Rifamycins list is much longer.
Drug Interactions cont.

- Studies suggest that the inhibitory effects of INH is outweighed by the inductive effect of RIF,
- so the overall effect of combined therapy with INH and RIF is to decrease the serum concentrations of the previously mentioned drugs,
- but probably not as great a decrease if rifampin was given by itself.
- Monthly Monitoring of drug levels

Common Side Effects and Toxicities

- INH – hepatitis, peripheral neuropathy, hypersensitivity, sleep and concentration difficulties, optic neuritis, arthralgias
- Rifampin – hepatitis, febrile reaction, rash, GI upset, thrombocytopenia (rare), pancreatitis
- Rifabutin – thrombocytopenia, hepatotoxicity, rash, 40% ability to react with other drugs compared to Rifampin. May be affected by other drugs
Common Side Effects and Toxicities

• PZA – hyperuricemia, hepatotoxicity, rash, arthralgias, nausea and vomiting
• Strep – nephrotoxic, VIII CN damage (ototoxic, hearing and vestibular)
• EMB – retrobulbar neuritis (decreased visual acuity (Snellen) and/or decreased red-green color discrimination (Ishihara), rash

Common Side Effects and Toxicities cont.

• Capreomycin – nephrotoxic, VIII CN damage (ototoxic)
• Amikacin/Kanamycin – two closely related drugs, similar toxicities as above, if resistant to one, usually resistant to the other.
• Ethionamide – hepatotoxic, GI distress, hypothyroidism, gynecomastia, acne, hair loss, menstrual irreg., need B6
• Cycloserine – psychosis, personality changes, rash, convulsions
• PAS – GI distress, hypersensitivity, sodium load, hepatotoxic, bleeding, hypothyroidism
Common Side Effects and Toxicities cont.

- Clofazimine – pink/red discoloration of skin/body fluids, GI, photosensitivity
- Moxifloxacin, Levofloxacin – GI upset, hypersensitivity, rash, dizziness, psychosis, agitation
- Augmentin – diarrhea and abd pain most common, hypersensitivity/rash, n/v
- Linezolid – myelosuppression, diarrhea, nausea and optic neuritis and peripheral neuropathy, expensive, B6

Case study 57yo cauc male

- S+C+, infiltrate RUL and apex, susceptible organism
- Tobacco 2ppd, hx. of daily alcohol use
- Baseline LFT’s normal
- 2-15-07 IRZE initiated
- 3-19-07 AST 362, ALT 380, T.bili 0.6, Serology negative for Hepatitis A, B & C
- 3-20-07 INH held, PZA discontinued due to hepatotoxicity and Moxi was added to R and E.
- 4-17-07 Moxi discontinued due to Abd pain and severe diarrhea (neg for C.diff), Rif and EMB cont.
- 4-23-07 AST 30, ALT 26
- 5-2-07 “all meds” held due to cont. abd pain and diarrhea
- 5-3-07 WBC’s 15.8, neutrophils 84, uric acid 18 (8), AST 99, ALT 66, patient hospitalized for acute abdomen and diagnosed with pancreatitis
57yo cauc male continued

- 5-7-07 discharged from the hospital with rifampin alleged to be the culprit.
- 5-16-08 AST 21, ALT 24, amylase 194(99), lipase 204(59), CBC normal
- 5-22-07 AST 20, ALT 17, amylase 107, lipase 92
- 5-23-07 INH reattempted x1 dose → N, V, and diarrhea → held
- ~5-26-07 EMB tried and after 10 days → diarrhea and abd pain → held, On no meds again
- Recommended GI consult to r/o hepatobiliary disorder- pt. refused.
- Heartland concurred with GI consult and stated patient would be ideal candidate to hospitalize until an effective regimen could be established- pt refused due to financial concerns.
- 6-18-07 AST 19, ALT 8, amylase 44, lipase 24
- 7-19-07 rifabutin and moxifloxacin was finally established and discontinued after 364 doses on 7-17-08.

57yo cauc male continued

- After one month of effective therapy it took almost 4 months to reestablish effective therapy.
- LFT’s and amylase, lipase q2wks for several months then monthly for remainder of therapy- all were normal
- Questions are:
  Did pt have pancreatitis before initiation of therapy or was it due to alcohol or the combination of alcohol and TB meds?
  Was it really the Rifampin? (Took Rifabutin for a year with no problems)
  Never was rechallenged with Rifampin.
References

- MMWR Treatment of Tuberculosis, 6-20-2003/vol.52/No.RR-11
- MMWR Targeted Tuberculin Testing and Treatment of Latent Tuberculosis Infection, 6-9-2000/Vol.49/No.RR-6
- Heartland National TB Center, Tuberculosis Core References for Clinicians
- Jamey “Todd” Braun RN, BSN, MPH, NMDH, Recognizing and Responding to Adverse TB Drug Events.ppt