Managing Side-Effects of TB Medications

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Inroduction

- Poisons and medicine are oftentimes the same substance given with different intents

  Peter Mere Latham 1789-1875 English physician & educator

Topics

- General considerations
- List of adverse effects of TB drugs
- Drug effects on liver
  - Drug metabolism by liver
  - Spectrum of drug effects on liver
  - Commonly used lab tests
  - Drug-specific effects on liver
  - Monitoring for toxicity
  - Management of drug effects on liver
  - Management of GI intolerance
- Dermatologic complications
- Neurologic complications
  - Includes optic (eye) and otic (ear) ones
- Individual drugs -other side effects

General Considerations

General Approach

- Recognize that treatment is difficult
  - Symptoms
    - Drug-related
    - Due to other causes – including TB itself
    - Fear of drugs
  - Serious adverse reactions
    - Need to be anticipated
    - Require monitoring for
    - May prompt discontinuation / changing medication

General Approach

- Essential elements of a TB program
  - Ready access to care for patients
  - Adequate education of staff
  - Good communication among staff, health care providers, patients
  - Standardized approaches
    - Patient education
    - Medical history form
    - Patient instructions
    - # of doses of medications dispensed at a time

General Approach

Continue drug

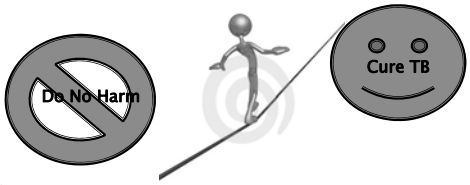
- Address, relieve symptoms
- Reassure patient
- Emphasize importance of Rx completion
- Be firm: treatment must be completed
- Make it a common goal to complete Rx on time

Stop drug

- Recognize signs & symptoms of drug toxicity
- Know when to stop / not administer drug
- Promptly report symptoms
- Communicate with physician, DOT worker, patient

General Approach

- Make every attempt to avoid unnecessary breaks in therapy
- Remind patient that breaks result in prolonged duration of treatment



Types of Adverse Effects of TB Drugs

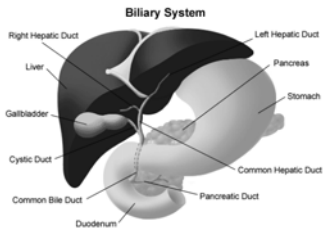
Serious Drug Complications

- Hepatotoxicity
- Hearing loss
- Kidney failure
- Vision loss
- Toxic skin / systemic reactions
- Hematologic (blood) reactions
- Electrolyte abnormalities
- Neurologic damage
- Death

Less Serious Complications

- Skin rash, itching
- Nausea, vomiting, diarrhea
- Reversible CNS symptoms
- Bone & joint symptoms
- Endocrine effects (less common)

Effects of Drugs on the Liver



Hepatic Drug Metabolism

Drug is swallowed

Absorbed from the GI tract into blood vessels

Enters liver via portal vein

Metabolized in liver

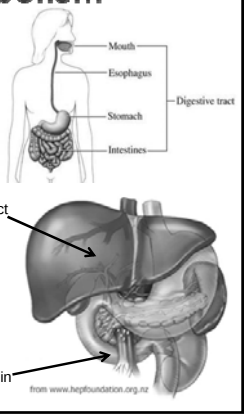
One process involves **cytochrome P450** class of enzymes

Rifampin Activates

Enters circulation or stored in bile

Bile enters duodenum

Drug is excreted in stool or reabsorbed (Enterohepatic Circulation)



Drug Effects on Liver: A Spectrum

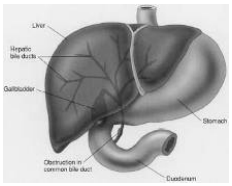
- Fulminant liver disease / death
  - 30% cases in US are caused by drugs
- Drug induced liver injury (DILI)
  - 700 drugs approved in US can cause liver toxicity
  - Important to detect early
- Hepatic adaptation
  - Protective response
- Cholestasis
  - Bile does not flow freely from liver to bowel
- Asymptomatic elevations in bilirubin

Lab Tests to Detect Liver Damage

- Liver cells and bile duct cells contain enzymes
  - Involved in metabolism of protein, amino acids
  - Released into blood if liver is damaged
- **ALT (SGPT)**
  - Released from damaged liver cells into blood
  - Most specific test for DILI
  - Can be elevated in hepatic adaptation
- AST (SGOT)
  - Released from damaged liver cells into blood
  - Not specific to liver (found in heart, muscle, RBCs)

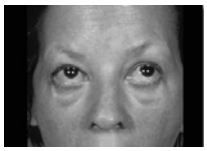
Lab Tests to Detect Bile or Bile Duct Problems

- Alkaline phosphatase
  - Enzyme found in liver cells & cells lining bile ducts
  - Elevated in bile duct obstruction, cholestasis, infiltrative diseases of liver
    - Elevated in children & pregnant women
- GGT
- 5' nucleotidase (5'NTD)



Jaundice

- Bilirubin
  - Results from the breakdown of red blood cells
  - Normally, it passes through the liver, is conjugated (made water soluble), & excreted in stool
  - When the liver cannot handle bilirubin normally or bile flow is impaired, bilirubin leaks into the blood stream
    - Causes jaundice or icterus



Hepatocellular Injury: Hepatic Enzymes ALT & AST

- ALT (SGPT) is more specific for hepatocellular injury than AST (SGOT)
- AST>ALT with alcohol-related disease
  - AST/ALT >2 suggests alcohol is the cause

TOAST

Hepatocellular Injury: Hepatic Enzymes ALT & AST

- 2.5% of normal, healthy people will have ALT "above upper limit of normal" (ULN)
  - Because "normal" levels defined as those within 2 standard deviations of the mean from a healthy population
- It is customary to compare multiples of ULN
  - Interlaboratory variation
  - Variation within an individual up to 45% in a day
- $\geq$ 3 times ULN with symptoms or $\geq$ 5 times ULN without symptoms is considered significant

INH

Saukkonen J, et al. An official ATS statement: hepatotoxiciy of antituberculosis therapy. Am J Respir Crit Care Med 2006;174:935-952

- Cleared in liver by acetylation
- Genetic variation => fast, slow, & intermediate acetylators
  - Significance unclear
  - Genotyping suggests slow acetylators develop higher peak ALT & more frequent elevations >3 X ULN than fast acetylators
    - Unknown significance
- Up to 20% people treated with INH alone have low-grade, transient, asymptomatic ALT increase – "hepatic adaptation"

INH

- Rate of hepatotoxicity when used alone: 0.1-0.6%
- Timing: weeks to months of starting drug
- Incidence & severity increases with age
- Risk increases with:
  - Chronic alcohol consumption
  - Active hepatitis B (+HBeAg)
  - Elevated baseline transaminases (AST, ALT)
  - Concomitant use of other hepatotoxic drugs
  - 3rd trimester pregnancy to 3 months post-partum
  - Pre-existing liver disease

Rifampin

- Dose-dependent interference with bilirubin uptake => subclinical, elevated **unconjugated** bilirubin & jaundice
  - May be transient
  - May occur early in treatment
- Can also cause asymptomatic elevation **conjugated** bilirubin (several mechanisms)

Rifampin Hepatotoxicity

- Hepatocellular injury less common
  - Insidious cholestasis
  - Anorexia, nausea, vomiting, fever, jaundice
  - Mildly elevated ALT, elevated bilirubin
  - Usually occurs in first month of treatment
  - RIF is much less likely to cause hepatoxicity than INH or PZA

Pyrazinamide

- Both dose-dependent & idiosyncratic hepatotoxicity
- Causes hepatotoxicity less often than INH ***but***
  - ***Can be more prolonged***
  - ***Can continue after drug discontinued***
  - ***Can be most severe***
- Can cause granulomatous hepatitis
  - Fever, rash, lymphadenopathy, elevated ALT

Monitoring for Hepatoxicity: LTBI

- Assess risk before treatment
- Baseline blood tests NOT generally recommended for healthy patients treated with INH or RIF alone
- Face-to-face clinical assessments are cornerstone of monitoring
- Obtain ALT & bilirubin at baseline & q 2-4 weeks for those with risk factors
  - Use ULN for ALT
- ALT is preferred marker for hepatotoxicity in those with symptoms

Hepatotoxicity: Special Considerations

- If baseline ALT > 3 times ULN screen for cause, assess risk for LTBI vs. risk for liver disease
- Test for HBeAg if ALT is elevated in those who are Hepatitis B surface antigen-seropositive
  - If HBeAg is +
    - Rifampin may be preferred
    - Consider referral for possible pre-treatment of Hepatitis B if ALT $\geq$ 2 times ULN
    - Monitor every 2-4 weeks clinically & with ALT

Management of Hepatotoxicity: LTBI

- Stop hepatotoxic drugs immediately for persistent nausea, vomiting, abdominal pain, unexplained fatigue. Contact physician. Measure ALT, bilirubin ASAP
  - For intermittent, transient symptoms administer drugs with food, reassure patient
- Withhold INH if ALT $\geq$3 times ULN if symptoms are present OR $\geq$5 times ULN without symptoms
- Rechallenge
  - If it is unclear that INH was the cause
  - INH was withheld before threshold was reached

Monitoring for & Managing Hepatotoxicity: Tuberculosis

- Obtain baseline ALT, AST, bilirubin, alkaline phosphatase, creatinine, platelet count on all adults
- Periodic monitoring for those with risk factors
- Drugs should not be discontinued for mild GI complaints
- Stop all hepatotoxic drugs if ALT is $\geq$ 3 times ULN with symptoms OR $\geq$ 5 times ULN without symptoms
- Substitute non-hepatotoxic drugs
- When ALT < 2 times ULN, reintroduce rifampin
- After 3-7 days, reintroduce INH
- Consider reintroducing PZA only if hepatotoxicity was not severe

GI Upset

- Improves if drugs are administered with food or closer to bedtime
- Ethionamide
  - Causes profound GI symptoms
  - Metallic taste, nausea, vomiting that can be severe, loss of appetite, abdominal pain
  - Dose-related
  - May give as split dose
- P-Aminosalicylic Acid (PAS)
  - Significant GI intolerance, less with granular formulation
  - Dose-related
- INH
  - Commercial liquid preparations contain sorbitol which can cause diarrhea

Skin Toxicity

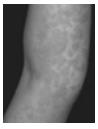
Dermatologic Reactions

- Itching with or without erythematous rash is common early side effect
  - May resolve after 1st several weeks of therapy without stopping medications
  - For mild or localized reaction, continue treatment & treat the rash and pruritis symptomatically – antihistamines, topical steroids
- Photosensitivity
  - PZA, fluoroquinolones

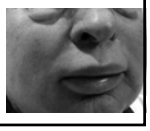
Hydroxyzine (Atarax®, Vistaril®)

- Indications
  - Itching: 25–100 mg every 6–8 hours
  - Nausea, vomiting: 25–100 mg every 4–6 hours (IM or PO)
  - Anxiety: 50–100 mg every 6 hours
  - Insomnia: 50–100 mg
- Maximum daily dose: 600 mg

Dermatologic Reactions

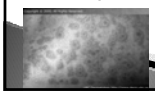


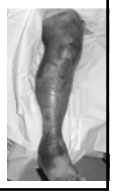
- Hives, urticaria, erythematous rash
  - Any drug
  - Stop all drugs immediately, re-challenge 1 at a time
    - Wait for rash to resolve
    - Start RIF 1st (least likely to be cause)
    - If no recurrence after 2–3 days, start INH
    - Continue with EMB or PZA
    - Discontinue any drug which causes recurrence
- Angioedema, anaphylaxis, or airway compromise
  - Stop drug – consider desensitization in ICU



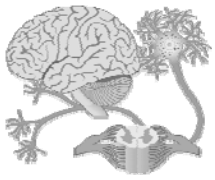
Other Serious Dermatologic Reactions

- Spectrum of diseases – generalized, involve mucus membranes, cause fever – epidermis separates from dermis
  - Stevens-Johnson Syndrome
  - Toxic Epidermal Necrolysis (severe form SJS)
- Mortality high
- Quinolones
- Emergency, hospitalization
- Stop offending drug, do not use again





Neurotoxicity



Neurotoxicity: Peripheral Neuropathy

- Numbness, tingling hands & feet in stocking-glove pattern
- Risk factors: diabetes, alcoholism, HIV, hypothyroidism, pregnancy, poor nutrition, inadequate dietary intake of pyridoxine
- Pyridoxine supplements
  - 10-50 mg daily (should this be routine?) for INH
  - 100-200 for cycloserine &/or ethionamide

Peripheral Neuropathy

- INH
  - Dose-related
  - Interferes with biologic function of vitamin B6
- Ethionamide
  - Increased incidence with prolonged use
- Linezolid
  - Increased incidence with prolonged use
  - 600 mg daily instead of twice daily is used to prevent this
- Ethambutol, cycloserine
  - Rare

CNS Effects

- INH
  - Inability to concentrate, irritability, dysarthria, seizures, dysphoria
- Cycloserine (my mnemonic – cyclo, psycho)
  - Headache, restlessness, psychosis, seizures (dose-related)
  - Pyridoxine 100-200 mg daily to prevent / treat
- Ethionamide
  - Anxiety, depression, psychosis
  - Increased incidence with prolonged treatment
- Fluoroquinolones
  - Dizziness, insomnia, tremulousness, headache

Vision – E – E Eye

- Ethambutol
  - Retrobulbar neuritis
  - Dose related – very rare (if at all) with currently recommended doses
  - Decreased red-green color discrimination (1 or both eyes), decreased visual acuity
  - ⬆ With renal disease
- Ethionamide
  - Optic neuritis
  - Dose related

Ototoxicity : 8th Cranial Nerve Damage

- Streptomycin (SM)
  - Vestibular (balance) and hearing disturbance
  - Related to single dose size and cumulative dose (>100–200 g)
  - Increased incidence if diuretics are used
  - Monitor with audiogram, Romberg
  - Hearing loss can be permanent – consider stopping
- Amikacin & Kanamycin
  - Less vestibular toxicity than SM
- Capreomycin

These drugs also cause nephrotoxicity & require monitoring

Ototoxicity: Aminoglycosides

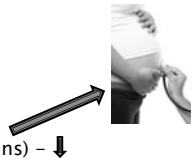
- Injectable agents – 15mg/kg daily or 25 mg/kg TIW
  - Ototoxicity often permanent
    - *Hearing loss $\geq$ 20 db occurred in 32/87 (37%) patients, 88% had persistent loss at end of follow-up
    - Associated with older age, duration of treatment, & total dose
    - Not associated with vestibular or renal toxicity
    - Amikacin>Kanamycin >Streptomycin
    - TIW = daily Rx

*Peloquin, et al. Aminoglycoside toxicity…Clin Inf Dis 2004;38:1538-44

Side Effects of Individual TB Drugs

Rifampin: Drug Interactions

- Rifampin induces cytochrome P450 class of enzymes
  - Involved in drug metabolism
- Rifampin interacts with
  - Narcotics (methadone) – ⇓
  - Corticosteroids – ⇓
  - Warfarin (coumadin®) – ⇓
  - Phenytoin (dilantin®) – ⇓
  - Oral contraceptives (estrogens) – ⇓
  - HIV protease inhibitors & nonnucleoside reverse transcriptase inhibitors – complex interactions



Rifampin: Hypersensitivity Reactions

- Flu-like syndrome with fever, chills, headache, & bone pain
  - Can begin 1-2 hrs after medication dose and resolve spontaneously after 6-8 hrs
  - More common in intermittent dosing, higher dose
  - Can try daily therapy if mild
- Severe immunologic reactions – rare, each < 0.1% patients
  - Low platelet count / petechiae
  - Kidney dysfunction
  - Hemolytic anemia
  - Thrombotic thrombocytopenic purpura

Rifampin

- Red-orange discoloration urine, tears, perspiration, feces
  - Can permanently discolor soft contact lenses

Pyrazinamide (PZA)

- Arthralgias common – Rx symptomatically
- Elevated uric acid
  - PZA is a pro-drug, converted to the active compound Pyrazinoic acid
  - Pyrazinoic acid blocks renal tubular excretion of uric acid => elevated uric acid
  - Allopurinol does not reverse this
  - Routine measurement of uric acid is not recommended
  - Gout is rare
  - Hyperuricemia without gout is not a reason for discontinuing drug

Ethionamide

- Endocrine disturbances
  - Gynecomastia, alopecia, hypothyroidism, impotence
  - Diabetes may be more difficult to manage
  - Acne
  - Irregular menstrual cycles

Capreomycin

- Electrolyte disturbances
  - Potassium, calcium, and magnesium depletion
- Proteinuria is common

Quinolones

- Tendonitis, tendon rupture – very rare
  - All ages
  - Greater risk age >60
  - Patients taking corticosteroids
  - Transplant patients
- QTc prolongation
- Nausea & diarrhea

PAS

- Hypothyroidism is common
  - Increased incidence when used with ethionamide
  - Reversible when drug stopped
  - Goiter can develop
- Malabsorption
  - Steatorrhea (fat malabsorption)
  - Doubling of prothrombin time
    - Vitamin K is a fat soluble vitamin
  - Levels of fat soluble vitamins (A, D, E) can be measured & monitored

Linezolid

- Myelosuppression
- Serotonin syndrome
- Nausea & diarrhea

Stuff Happens; Be Prepared