Why TB Drugs Fail

Part 2

OR

How We Fail TB Drugs
(and Tb Patients)
PROBLEMS IN TX

• FAILURE TO RESPOND
• TB MENINGITIS
• RENAL FAILURE
• HEPATITIS
• CAN’T SWALLOW PILLS
• GI INTOXICITY
• ADVERSE DRUG REACTIONS
• ALLERGIES
• DRUG INTERACTIONS

CASE STUDY

• JB is a 42 yo BM who was admitted to hospital following a new onset seizure. He complains of persistent headaches over the past month and a history of 30 lb weight loss and chronic cough. He is diabetic and has a history of alcoholism.
• He has a negative PPD but an abnormal chest x-ray and AFB positive sputum smears and culture.
CASE STUDY

- JB is started on 4-drug TB therapy and referred to his CHD.
- JB does well and is smear and culture negative at 2 months. EMB and PZA are stopped.
- However, at 3 months he is again losing weight, his headaches have returned and he is now smear and culture positive.

Question 1

- The most likely reason for JB’s treatment failure is:
  - 1. Non compliance
  - 2. Resistance
  - 3. Low serum drug levels
  - 4. Inadequate tissue penetration
Diabetes

- Reduced immunity
- Changes in GI emptying/absorption
- Effects of severe hyperglycemia
  - Altered protein binding
- TB and TB drugs can make diabetes more difficult to control
- Some antidiabetic drugs can contribute to hepatitis

Alcohol/Drug Abuse

- Gastritis
- Effect on metabolism
- Malnutrition
- Decreased immunity
- Increased risk of side effects
  - Hepatitis
  - Peripheral neuropathy
- Non-compliance
THICK WALLED CAVITY

QUESTION #2

• JB had an MRI and his CNS TB has gotten worse. Which drug would NOT be a good choice to cross the BBB in therapeutic quantities?
  – 1. INH
  – 2. RIFAMPIN
  – 4. ETHAMBUTOL
  – 4. PZA
  – 5. STREPTOMYCIN
TB MENINGITIS

Tuberculoma-biopsy proven-with surrounding edema
### MIC Versus Concentration

<table>
<thead>
<tr>
<th>DRUG</th>
<th>PK [ ] MCG/ML</th>
<th>MCG/ML MIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>INH</td>
<td>3 – 5</td>
<td>0.01 – 0.25</td>
</tr>
<tr>
<td>RIF</td>
<td>8 – 24</td>
<td>0.06 – 0.25</td>
</tr>
<tr>
<td>PZA</td>
<td>20 – 60</td>
<td>6.2 – 50</td>
</tr>
<tr>
<td>EMB</td>
<td>3 – 5</td>
<td>0.5 – 2.0</td>
</tr>
<tr>
<td>STM</td>
<td>35 – 45</td>
<td>0.25 – 2.5</td>
</tr>
<tr>
<td>CAP</td>
<td>35 – 45</td>
<td>1.25 – 2.5</td>
</tr>
<tr>
<td>OFLOX</td>
<td>8 – 10</td>
<td>0.25 – 2.0</td>
</tr>
</tbody>
</table>

### CNS PENETRATION

- **INH** 90 - 100 %
- **RIF** 10 - 25%
- **PZA** 75 - 100%
- **EMB** 10 - 50%
- **STM** <10%
- **QUINILONES** 10 - 50%
- **CYCLOSERINE** 80 - 90 %
### Protein Binding

<table>
<thead>
<tr>
<th>Drug</th>
<th>Expected Serum [MCG/ML]</th>
<th>PB</th>
<th>Effective Serum [MCG/ML]</th>
<th>% CSF Normal</th>
<th>Effective conc norm</th>
<th>% CSF Inflamed</th>
<th>Effective CSF [M] Inflamed</th>
<th>MIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aminoglycoside</td>
<td>~30%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cipro/Floxin</td>
<td>20 - 40%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EMB</td>
<td>10 - 15%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>INH</td>
<td>10 - 15%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PZA</td>
<td>50%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PAS</td>
<td>50 - 60%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RIF</td>
<td>84 - 90%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
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### CNS Penetration

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<th>Effective CSF [M] Inflamed</th>
<th>MIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>INH</td>
<td>3 - 5 (4)</td>
<td>10 - 15%</td>
<td>3.4</td>
<td>100%</td>
<td>4</td>
<td>100%</td>
<td>4</td>
<td>0.2</td>
</tr>
<tr>
<td>RIF</td>
<td>8 - 24 (10)</td>
<td>85%</td>
<td>1.5</td>
<td>10%</td>
<td>1</td>
<td>20%</td>
<td>2</td>
<td>0.5</td>
</tr>
<tr>
<td>EMB</td>
<td>2 - 6 (4)</td>
<td>25%</td>
<td>3</td>
<td>0 - 10%</td>
<td>6.4</td>
<td>90%</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>PZA</td>
<td>20 - 60 (40)</td>
<td>50%</td>
<td>20</td>
<td>75%</td>
<td>30</td>
<td>100%</td>
<td>40</td>
<td>20</td>
</tr>
<tr>
<td>LEVOFLOXACIN</td>
<td>8 - 12 (10)</td>
<td>30%</td>
<td>7</td>
<td>15 - 20%</td>
<td>2</td>
<td>45%</td>
<td>4.5</td>
<td></td>
</tr>
<tr>
<td>MOXIFLOXACIN</td>
<td>3 - 5 (4)</td>
<td>40%</td>
<td>1.6</td>
<td></td>
<td></td>
<td>50%</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>CYCLOSERINE</td>
<td>20 - 35 (25)</td>
<td>0%</td>
<td>25</td>
<td>90%</td>
<td>22.5</td>
<td>100%</td>
<td>25</td>
<td></td>
</tr>
</tbody>
</table>
LOW SERUM DRUG LEVELS

• WRONG DOSE
• REDUCED ABSORPTION
  – DIABETES/HIV
  – GI DISEASE/SURGERY
  – MALNUTRITION
  – LAXATIVE ABUSE
  – DRUG-FOOD INTERACTIONS
  – DRUG-DRUG INTERACTIONS

• INCREASED METABOLISM / EFLUX
• VOMITING
• NON-COMPLIANCE
INTESTINAL WALL

- SMALL INTESTINE
  - PAPILLI

P-Glycoproteins

Fig. 5 - Location of P-Glycoprotein in the apical membrane of a typical epithelial intestinal cell

www.liv.ac.uk/hivgroup/research/pgp.html
QUESTION #3

• WHICH OF THE FOLLOWING CAN BE TAKEN WITHOUT REGARD TO MEALS?
  – 1. INH
  – 2. RIFAMPIN
  – 3. MOXIFLOXACIN
  – 4. ETHAMBUTOL
Bioavailability

- RIF 100%(FASTING) – 70% (FED)
- NFV 20%(FASTING) – 80% (FED)

Absorption – Food/Drug Interactions

- Most often caused by
  - Iron
  - Calcium
  - Magnesium
  - Aluminum
  - Zinc
  - Fat
  - Low/high pH
  - Protein

- Most effected
  - INH, EMB, RIF
  - Ofloxacin/ciprofloxacin
  - Indinavir, saquinavir, nelfinavir, lopinavir, ddl, tenofovir
BEWARE OF FLUIDS

• DAIRY PRODUCTS
  – Ca FORMS INSOLUBLE COMPLEXES WITH RX
• FOOD SUPPLEMENTS
  – Protein, Ca and other minerals
• ORANGE JUICE
  – MG AND CA
• APPLE JUICE
  – CA AND FE

TUBE FEEDINGS

• STOP FEEDING FOR 2 HOURS BEFORE AND AFTER TB DRUGS
TAKE ON AN EMPTY STOMACH

(1 HR BEFORE OR 2 HRS AFTER A MEAL)

INH
RIF, RBT
EMB
PZA
QUINOLONES

TAKE WITH FOOD

• ETHIONAMIDE / PAS
  – TO REDUCE GI SIDE EFFECTS

• CLOFAZAMINE
  – TO MAXIMIZE ABSORPTION
WITHOUT REGARD TO MEALS

- PZA
- CYCLOSERINE
- RIFAPENTINE
- MOXIFLOXACIN
Resistance

• Primary mixed resistance
• Secondary resistance
  – Risk factors
    • Patient non-compliance
    • Improper prescription
    • Inadequate tissue penetration
    • Heavy burden of disease

RESISTANCE

– LOW DRUG LEVELS
  • IN SERUM vs AT SITE OF INFECTION
  • DRUG INTERACTION
  • VOMITING
RESISTANCE POTENTIAL

Population Curve
Question #4

• Shortly after his MRI, JB’s lab work shows rapidly deteriorating renal function. His $\text{CL}_{\text{cr}}$ is currently 20 ml/min. Which drug may need to have its’ dose modified?

1. INH
2. RIF
3. EMB
4. PZA

DRUGS NEEDING ADJUSTMENT IN RENAL FAILURE

• EXCRETED RENALLY AS
  – ACTIVE DRUG
  – ACTIVE METABOLITE
  – POTENTIALLY TOXIC METABOLITE

• HOW ADJUST DOSING?
  – REDUCE DOSE
  – EXTEND DOSING INTERVAL

• WHEN ADJUST?
  – 50, 30, 10 ML/MIN AND SOMETIMES AT 80
RENAL DOSING

• ISONIAZID
  – ACUTE RENAL FAILURE IN OVER DOSE
  – $\text{CL}_{\text{CR}} < 10$, REDUCE DOSE BY 50%

• RIFAMPIN
  – CAN CAUSE ACUTE RENAL FAILURE
  – $\text{CL}_{\text{CR}} < 10$, REDUCE DOSE BY 50%

RENAL DOSING

• AMINOGLYCOSIDES
  – SM, AMK, KAN, CAP
  – CAUSE RENAL TOXICITY
    • REDUCE DOSE AT 80 ML/MIN, 50, AND 10
    • OR EXTEND DOSING INTERVAL

• EMB
  – RENALLY EXCRETED AS ACTIVE DRUG
  – REDUCE DOSE AT 50 ML/MIN, 10 ML/MIN
RENAL DOSING

• PZA
  – DOSE CHANGES NOT GENERALLY REQUIRED BUT -
    • CL_{CR} < 50 REDUCE DOSE TO 12-20 MG/KG/D
    • EXTEND INTERVAL AT 10 ML/MIN
    • DIALYSIS – AVOID USE

• RIFABUTIN
  – CL < 30 ML/MIN REDUCE DOSE BY 50%

• QUINALONES
  – OFLOXACIN, LEVOFLOXACIN
    • REDUCE DOSES AT 50 ML/MIN
    • EXTEND INTERVAL AT 10 ML/MIN
  – MOXIFLOXACIN
    • NO DOSAGE ADJUSTMENT NEEDED

• CYCLOSERINE
  • REDUCE DOSE AT 80, 50, 10 ML
HEMODIALYSIS

• CAN GENERALLY GIVE STANDARD DAILY DOSES 3 TIMES A WEEK AFTER DIALYSIS
• MAY GET DIALYSIS UNIT TO DO DOT FOR YOU
• DO DRUG LEVELS

RENAL FAILURE

• USE DRUGS METABOLIZED BY LIVER
  – INH, RIF, PZA
  – MOXIFLOXACIN VS LEVOFLOXACIN
• GIVE LOWER DOSES OF DRUGS RENALLY EXCRETED AS ACTIVE AGENTS
• GIVE SAME DOSE LESS FREQUENTLY
  – DAILY DOSE 2 OR 3 TIMES A WEEK
• GIVE AFTER DIALYSIS
• MONITOR
CASE

• JB is successfully treated with steroids for his contrast related renal failure. Three weeks later he develops elevated AST and ALT (>5x uln) and his total billi is at 4 and increasing.

HEPATIC DYSFUNCTION

• ALLOW LIVER TO COOL OFF
• USE RENALLY EXCRETED DRUGS
  – EMB, QUINALONE, AMG
• RESTART SUSPECT DRUGS ONE AT A TIME
• RIFABUTIN VS RIFAMPIN
• GIVE TWICE WEEKLY DOSES
• LEVOFLOXICIN VS MOXIFLOXACIN
• ADJUNCT AGENTS
  – ACTIGALL
  – INTERFERON ALFA
• MONITOR
PROBLEMS IN TX

- FAILURE TO RESPOND
- TB MENINGITIS
- RENAL FAILURE
- HEPATITIS
- NON-COMPLIANCE
  - PSYCHIATRIC ISSUES/ SUBSTANCE ABUSE
  - CAN’T SWALLOW PILLS
  - GI INTOLERANCE
  - ADVERSE DRUG REACTIONS
  - ALLERGIES
  - DRUG INTERACTIONS
DOT

• DIRECTLY OBSERVE PATIENT TAKING THE MEDICATION

DOT - OR - DOD?

• DOD
  – DIRECTLY OBSERVED DELIVERY
CAN’T SWALLOW PILLS

• CRUSH OR USE ORAL LIQUIDS
  – INH SYRUP
  – RIF
    • SIMPLE SYRUP
    • JAM, HONEY, APPLESAUCE, ETC
    • STABILITY ?
  – PZA, EMB
    • SIMPLE SYRUP
    • CRUSH IN JELLY, APPLE JUICE

CAN’T SWALLOW

• INJECTABLES
  – INH
  – RIF
  – AMINOGLYCOSIDES and CAPREOMYCIN
  – QUINILONES
  – EMB
• SUPPOSITORIES
GI INTOLERANCE

- Divide doses
- Start with low dose and increase over several days
- Give after meals
- Medicate
  - H2 Antagonist/ PPI
  - Metoclopramide
  - Promethazine
  - Zofran
  - Lorazepam
- PEJ Tube

ADR

- High uric acid levels
  - Allopurinol, Colchicine, Probencid
- Myalgias, Arthralgias
  - NSAIDs
  - Exercise
ADR

• GIVE AT BEDTIME
• SWITCH TO A DIFFERENT DRUG
• ALLERGY/ITCHING
  – ANTIHISTAMINES
  – STEROIDS
  – DESENSITIZATION

ALLERGIES

• DESENSITIZATION
  – LOW DOSES GIVEN FREQUENTLY AND IN GRADUALLY INCREASING DOSES

  – DO ONLY WHERE EMERGENCY TX IS AVAILABLE
DRUG INTERACTIONS

• PHENYTOIN
• WARFARIN
• HORMONE BASED CONTRACEPTIVES
• EFAVIRENZ
• HIV PROTEASE INHIBITORS

QUESTION #5

• Which team is going to win the SEC championship?
  – Florida Gators
  – Alabama Tide
  – The what?
Jenifur waiting for the big game to start

TB Hotline
1-800-4TB-INFO
THE END
A.G. HOLLEY TB HOTLINE
1-800-4TB-INFO