Pharmacology and Pharmacokinetics of TB Drugs Part I

Charles A. Peloquin, Pharm. D.
Professor, and Director
Infectious Disease Pharmacokinetics Laboratory
College of Pharmacy and
The Emerging Pathogens Institute
University of Florida
Drugs FDA Approved for TB

- Aminosalicylate sodium (PAS)
- Capreomycin
- Cycloserine
- Ethionamide
- Ethambutol
- Isoniazid
- Pyrazinamide
- Rifampin
- Rifapentine
- Streptomycin
Drugs not FDA approved for TB

Other Aminoglycosides:
- Amikacin
- Kanamycin

Fluoroquinolones:
- Moxifloxacin
- Levofloxacin
Drugs not FDA approved for TB

Macrolides - generally poor TB drugs:
- Azithromycin
- Clarithromycin
  (indicated for, and primarily useful for, MAC)

- Amoxicillin-clavulanate (role not established)
- **Clofazimine** (role being re-evaluated)
- **Rifabutin** (used for TB and MAC)
- **Linezolid**, newer agents Sutezolid and AZD-5847

Outside US: prothionamide, thiacetazone, viomycin
Pretomanid (PA-824)

- Unique mechanism of action
- Narrow spectrum of activity
- Bactericidal activity in mouse models

<table>
<thead>
<tr>
<th>MIC vs. <em>M. tuberculosis</em> H37Rv (µg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid</td>
</tr>
<tr>
<td>PA-824</td>
</tr>
<tr>
<td>Rifampin</td>
</tr>
</tbody>
</table>

1Stover et al, Nature (2000); 405:962
2Tyagi et al, AAC (2005); 49:2289
3Lenaerts et al, AAC (2005); 49:2294
Delamanid (OPC-67683)

- Nitroimidazo-oxazole
- Cross-resistant with PA-824
- Up to 20x more potent than PA-824
- As with PA-824, best companion drug is PZA

<table>
<thead>
<tr>
<th></th>
<th>MIC (mg/L)</th>
<th>MBD (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>INH</td>
<td>0.1</td>
<td>10</td>
</tr>
<tr>
<td>RIF</td>
<td>0.4</td>
<td>10</td>
</tr>
<tr>
<td>OPC-67683</td>
<td>0.012</td>
<td>2.5</td>
</tr>
<tr>
<td>PA-824</td>
<td>0.2</td>
<td>20+</td>
</tr>
</tbody>
</table>

MIC = Minimum inhibitory concentration
MBD = Minimum bactericidal dose (ie, to kill 99% of bacteria)

Otsuka Pharmaceutical Inc.,
Presented at ICAAC, December, 2005
Bedaquiline (TMC207)

Class: Diarylquinoline
• Median MIC = 0.06 µg/ml
• New target: ATP synthase
• Selective activity vs. mycobacteria (including NTM)
• No cross-resistance

Cole & Alzari, Science 2005; 307:214
Isoniazid (INH)

- **Role:** primary drug, along with rifampin
- **Action:** inhibits cell wall synthesis
- **Dosage:** oral, I.M., I.V. (in normal saline only)
- **Dose:** 300 mg QD // 10-20 mg/Kg for kids
- **Cleared:** liver >> kidneys
- **Toxicity:** hepatotoxicity, peripheral neuropathy
Rifampin (RIF)

**role:** primary drug, along with INH

**action:** DNA-dependent RNA polymerase

**dosage:** oral, I.V.

**dose:** 600 mg QD // 10-20 mg / Kg for kids

**cleared:** liver >> kidneys

**toxicity:** hepatotoxicity, flu-like syndrome
Rifapentine (RPNT)

role: primary drug, along with INH
action: DNA-dependent RNA polymerase
dosage: oral
dose: 600 mg QD // moving to 1200 mg QD
cleared: liver >> kidneys
toxicity: hepatotoxicity, flu-like syndrome
Rifabutin (RBN)

- **role:** instead of RIF for HIV+ patients
- **action:** DNA-dependent RNA polymerase
- **dosage:** oral
- **dose:** 300 mg (150 - 450 mg) QD
- **cleared:** liver >> kidneys
- **toxicity:** neutropenia, thrombocytopenia, uveitis
# Rifamycin Comparison

<table>
<thead>
<tr>
<th></th>
<th>CYP 3A4 induction</th>
<th>Unique features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rifampin</td>
<td>1.00</td>
<td>flu-like syndrome</td>
</tr>
<tr>
<td>Rifapentine</td>
<td>0.85 to 1.00+</td>
<td>99% protein bound</td>
</tr>
<tr>
<td>Rifabutin</td>
<td>0.40</td>
<td>uveitis, neutropenia</td>
</tr>
</tbody>
</table>
## Rifamycin Comparison

<table>
<thead>
<tr>
<th></th>
<th>MIC * (µg/ml)</th>
<th>Cmax ^ (µg/ml)</th>
<th>Ratio</th>
<th>t ½ (hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rifampin</strong></td>
<td>0.25</td>
<td>12</td>
<td>48</td>
<td>3</td>
</tr>
<tr>
<td><strong>Rifapentine</strong></td>
<td>0.06</td>
<td>12</td>
<td>200</td>
<td>15</td>
</tr>
<tr>
<td><strong>Rifabutin</strong></td>
<td>0.06</td>
<td>0.6</td>
<td>10</td>
<td>36</td>
</tr>
</tbody>
</table>

* 7H12 broth  ^ total Rx (free and bound)
# Rifamycin Comparison

<table>
<thead>
<tr>
<th></th>
<th>MIC * (µg / ml)</th>
<th>Cmax # (µg / ml)</th>
<th>Ratio</th>
<th>t ½ (hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rifampin</td>
<td>0.25</td>
<td>1.8</td>
<td>7.2</td>
<td>3</td>
</tr>
<tr>
<td>Rifapentine</td>
<td>0.06</td>
<td>0.12</td>
<td>2.0</td>
<td>15</td>
</tr>
<tr>
<td>Rifabutin</td>
<td>0.06</td>
<td>0.09</td>
<td>1.5</td>
<td>36</td>
</tr>
</tbody>
</table>

* 7H12 broth # free Rx (only free is active)
role: primary drug, first 2 months
action: via metabolite pyrazinoic acid
dosage: oral
dose: 25 - 30 mg / Kg QD ( adults and kids )
cleared: liver, then metabolites via kidneys
toxicity: hepatotoxicity, elevated uric acid
Ethambutol (EMB)

role: “fourth drug” in case of resistance

action: inhibits cell wall synthesis

dosage: oral, (I.V. in Europe)

dose: 15 - 25 mg / Kg QD (adults and kids)

cleared: kidneys >> liver

toxicity: ocular toxicity, rashes
Streptomycin (SM)

role: “fourth drug” in case of resistance
action: inhibits protein synthesis
dosage: I.M., I.V.
dose: 12 - 15 mg / Kg QD (adults and kids)
cleared: kidneys
toxicity: ototoxicity, nephrotoxicity, cation loss
Amikacin (AK)
Kanamycin (KM)
Capreomycin (CM) *

role: drug resistant TB
action, PK, toxicity: same as streptomycin

* CM is a polypeptide
Levofloxacin (Levo)

role: drug resistant TB
action: inhibits DNA gyrase
dosage: oral, I.V.
dose: 750 - 1000 mg QD
cleared: kidneys
toxicity: caffeine like effects, GI, tendonitis
| **role:** | drug resistant TB |
| **action:** | inhibits DNA gyrase |
| **dosage:** | oral, I.V. |
| **dose:** | 400 mg QD |
| **cleared:** | kidneys and liver |
| **toxicity:** | caffeine like effects, GI, tendonitis |
Ethionamide (ETA)

role: drug resistant TB

action: inhibits cell wall synthesis

dosage: oral

dose: 250 - 500 mg BID //

10 - 20 mg / Kg divided BID for kids

cleared: liver

toxicity: GI upset, hypothyroidism
p-Aminosalicylic Acid (PAS)

role: drug resistant TB
action: not known
dosage: oral
dose: 4000 mg BID - TID //
       150 mg / Kg divided BID - TID for kids
cleared: liver >> kidneys
toxicity: GI upset, hypothyroidism
Cycloserine (CS)

role: drug resistant TB

action: inhibits cell wall synthesis

dosage: oral

dose: 250 - 500 mg BID / /

10 - 20 mg / Kg divided BID for kids

cleared: kidneys

toxicity: lack of concentration, altered behavior
How Do Antibiotics Work?

A drug must enter the organism, bind to a specific target, and produce an inhibitory or lethal effect.

Unless the drug is delivered to the site of infection (PK), nothing happens (PD).
PK and PD

- Pharmacokinetics (conc. vs time)
- Pharmacodynamics (conc. vs effect)
- PK/PD effect vs time
Pharmacodynamics (PD)

Concentration-Time Profile Following Oral Administration

- Concentration
- Onset time
- $t_{max}$
- $C_{max}$
- Duration of action
- Therapeutic Range
- MTC
- MEC
- AUC
Pharmacokinetics (PK)

The study of the **movement of drugs** through the body.

Most commonly based on the study of serum concentrations in relation to dose, with interpretation and dose adjustment.
**PK: Plasma Elimination Half-Life**

$t_{1/2}$ is defined as the time for concentrations (in plasma) to decline by 50%.

After 7 $t_{1/2}$s, nearly all of the drug is gone, regardless of the starting concentration.

t $1/2$ is independent of dose and concentration.
PK: Clearance

t 1/2 is inversely proportional to the clearance of a drug (Cl).

Clearance can be thought of as the size of the drain in the bathtub.

A big drain will empty the tub faster.
PK: Clearance

Clearance organs:

Kidneys: especially water soluble drugs
- creatinine clearance might predict

Liver: metabolize drugs to make water sol.
- AST, ALT usually do not predict

[ minor: lungs, skin, saliva... ]
PK: Volume of Distribution

t $1/2$ is directly proportional to the volume of distribution (V).

V can be viewed as the size of the bathtub. Big tubs take a longer time to drain.

t $1/2$ is viewed as a proportionality constant, dependent upon CI and V.
PK: Volume of Distribution

Large volumes of distribution typically reflect drug penetration into tissues which return the drug to the plasma space only slowly.

Drug molecules inside of tissues are unavailable to the organs of clearance.
PK: Data Handling

The most common parameters clinically are are Cmax (peak), Cmin (trough), Tmax, & t1/2.

Simple kinetics can be done with a calculator, or with a spreadsheet.

The most common calculations involve linear regression (fitting a straight line to data).
<table>
<thead>
<tr>
<th>Two Sample</th>
<th>Infusion</th>
<th>Ln Conc</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conc</td>
<td>Hrs post dose</td>
<td></td>
</tr>
<tr>
<td>26.30</td>
<td>2.00</td>
<td>3.27</td>
</tr>
<tr>
<td>9.40</td>
<td>6.00</td>
<td>2.24</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Slope</th>
<th>Intercept</th>
<th>ke</th>
<th>t 1/2</th>
<th>Cmax</th>
<th>Cmax intercept</th>
</tr>
</thead>
<tbody>
<tr>
<td>-0.26</td>
<td>3.78</td>
<td>0.257</td>
<td>2.69</td>
<td>43.99</td>
<td>43.99</td>
</tr>
</tbody>
</table>
Pharmacodynamics (PD)

the study of the relationships between drug concentrations and responses

Methods

• *in vitro* models
• animal models
• human clinical trials with dose escalation
Evans, 1986

![Graph showing the relationship between drug concentration and probability of response or toxicity. The x-axis represents Drug Concentration (μg/ml) ranging from 0 to 40, and the y-axis represents Probability (%) ranging from 0 to 100. A yellow curve indicates the response, while a white curve indicates toxicity.](#)
Minimal inhibitory concentration (MIC)

The concentration of the drug required to inhibit the growth of an organism in the laboratory.

From this: “susceptible” or “resistant”

[This test cannot be done within the patient.]
ID: Usual PK - PD Response Parameters

- Cmax / MIC
- Time > MIC
- AUC > MIC
**PD: Response Parameters**

- **Cmax** = 9 mcg / ml
- **MIC** = 3 mcg / ml
- **Cmax / MIC** = 3
- **T > MIC** = 8 h
- **AUC** (mcg * h / ml)
ETHIONAMIDE

TIME
CONC

eta

MIC
Pharmacodynamics (PD)

Killing of TB by most TB drugs can be described very well using AUC / MIC, and more AUC is better.

This has been known for many years, and has been widely published.
“Concentration-dependent” antimicrobials best given as large (daily) doses

- aminoglycosides, quinolones, RIFAMYCINS (based on *in vitro*, animal and human data)

- target a \( \frac{C_{\text{max}}}{\text{MIC}} \) of at least 10 - 12
Rifampin has profound concentration – dependent killing

<table>
<thead>
<tr>
<th>Week</th>
<th>5 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung week 1</td>
<td>100,000,000</td>
</tr>
<tr>
<td>Lung week 10</td>
<td>10,000</td>
</tr>
<tr>
<td>% reduction</td>
<td>99.99000%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Week</th>
<th>10 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung week 1</td>
<td>100,000,000</td>
</tr>
<tr>
<td>Lung week 10</td>
<td>100</td>
</tr>
<tr>
<td>% reduction</td>
<td>99.99990%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Week</th>
<th>20 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung week 1</td>
<td>100,000,000</td>
</tr>
<tr>
<td>Lung week 10</td>
<td>10</td>
</tr>
<tr>
<td>% reduction</td>
<td>99.99999%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Week</th>
<th>40 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung week 1</td>
<td>100,000,000</td>
</tr>
<tr>
<td>Lung week 10</td>
<td>0</td>
</tr>
<tr>
<td>% reduction</td>
<td>100.00000%</td>
</tr>
</tbody>
</table>

PD: Sterilizing Activity of Rifampin

Mean value after 600 mg oral dose

Jayaram et al, AAC (2003); 47:2118
# Rifampin 600 mg in Humans

<table>
<thead>
<tr>
<th>Cumulative percentage culture negative:</th>
</tr>
</thead>
<tbody>
<tr>
<td>month</td>
</tr>
<tr>
<td>----------------------</td>
</tr>
<tr>
<td>HRZS QD</td>
</tr>
<tr>
<td>HRZE QD</td>
</tr>
</tbody>
</table>

H 300 mg, S 750 mg, isoniazid
streptomycin
Z 35 mg / Kg, pyrazinamide
E 25 mg / Kg ethambutol

### Rifampin 1200 mg in Humans

<table>
<thead>
<tr>
<th>Cumulative percentage culture negative</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>month</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HRS QD</td>
<td>72</td>
<td>94</td>
<td>98</td>
</tr>
<tr>
<td>HRS QOD</td>
<td>70</td>
<td>93</td>
<td>100</td>
</tr>
</tbody>
</table>

### Isoniazid and Streptomycin

- **H 900 mg**, **S 1000 mg** QD both regimens

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### Rifampin 600 mg vs. 1200 mg

<table>
<thead>
<tr>
<th>Cumulative percentage culture negative</th>
<th>month</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>HRZS QD</td>
<td>38</td>
<td>77</td>
<td>97</td>
<td></td>
</tr>
<tr>
<td>R 600 mg, with Z</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HRS QD</td>
<td>72</td>
<td>94</td>
<td>98</td>
<td></td>
</tr>
<tr>
<td>R 1200 mg, NO Z</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>INH 900 mg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Rifampin 1200 mg

Flu-like syndrome was NOT reported by Kreis et al (3 months of treatment).

Even with highly-intermittent RIF, syndrome usually appears after 3 to 6 months.

Association between Acquired Rifamycin Resistance and the Pharmacokinetics of Rifabutin and Isoniazid among Patients with HIV and TB [Study 23A].


Clinical Infectious Diseases 2005; 40: 1481 - 1491.
Lesser INH AUC in Study 23A ARR versus 23A cure versus 22PK cure and HIV-seronegative

P = 0.0002, Kruskal-Wallis

Isoniazid dose 15 mg/kg to 900 mg, prospective PK
* P-Value by Mann-Whitney
Lesser rifabutin AUC with ARR versus cure

<table>
<thead>
<tr>
<th>Group</th>
<th>No.</th>
<th>Dose mg/kg Med (IQC)</th>
<th>$\text{AUC}_{0-24}$ Med (IQC)</th>
<th>P-Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARR</td>
<td>6</td>
<td>4.6 (3.5 - 5.7)</td>
<td>3.1 (2.0 - 3.8)</td>
<td>0.04</td>
</tr>
<tr>
<td>CURE</td>
<td>82</td>
<td>4.8 (4.2 – 6.2)</td>
<td>5.1 (4.0 - 7.4)</td>
<td></td>
</tr>
</tbody>
</table>

* P for RBT AUC ARR vs. cure, Mann-Whitney
Not all TB drugs are FDA-approved for TB

“Second-line” TB drugs are second line because of poor PK-PD profiles.

To use TB drugs safely, you must understand how they are absorbed and eliminated.
Rifamycins, in particular rifampin, currently are under-dosed. Higher doses are very likely to produce better bacteriological results. New clinical studies are underway to prove this.
Recent TB studies demonstrate that poor drug absorption (poor PK–PD) is associated with poor TB outcomes.
End Part I