Pharmacokinetics (PK) and Pharmacodynamics (PD) in the Treatment of Tuberculosis

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Disclosure:
Past employee & current stockholder of Johnson & Johnson Family of Companies

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Disclosures

• Johnson & Johnson: Stockholder
Same as it ever was….
Yeah, the twister comes
Here comes the twister
Same as it ever was….

- *Once in a Lifetime*, Talking Heads\(^1\)

Learning Objectives

At the end of this presentation, the learner will be able to:

• Describe the basic concepts of PK/PD, specifically:
  – the fundamentals of PK
  – the difference between PK and PD

• Describe the use of PK / PD principles in TB therapy, in particular, related to these in the use of:
  – INH
  – Rifamycins
  – Aminoglycosides

• Discuss the use of Clinical PK / Therapeutic Drug Monitoring in TB in relation to:
  – Optimizing efficacy
  – Minimizing toxicity
  – Patients needing it most
Intro to PK and PD

• **Pharmacokinetics (PK):**
  – **ADME:** Study of the time course of Absorption, Distribution, Metabolism & Excretion.

• **Clinical Pharmacokinetics**
  – The application of PK principles to the safe and effective therapeutic management of drugs in an individual patient
  – aka *Therapeutic Drug Monitoring (TDM)*

• **Pharmacodynamics (PD)**
  – Relationship between drug concentration at the site of action and the resulting *effect*

Pharmaco-KINETICS

Prescribed Dosing Regimen

Drug at Site of Action

Drug Effects

- Dosing & med errors
- Absorption
- Tissue & body fluid mass and volume
- Drug interactions
- Elimination
- Drug metabolism
- Adherence

- Genetic factors
- Drug interactions
- Tolerance
- Drug receptor status
- Effect of drug

COMBOS

Pharmacokinetics 101

• Assume plasma/serum concs = concs at site
• Bioavailability / Absorption
  – Drug properties
  – Pt factors
  – Drug / food interactions
• Vol of Dist (Vd): dosing proportional to Vd
  – Drug properties
  – Pt factors

Pharmacokinetics 101

• Clearance (volume / time):
  measure of removal of drug from plasma

\[
C_{in} \quad \text{Organs of Elim'n (Kidneys, Liver)} \quad C_{out}
\]

Blood flow

Elimination

Blood flow

Pharmacokinetics 101

• **Half-life** ($T_{1/2}$):
  - Time for concs to decrease by 50%
  - $T_{1/2}$ is independent of dose and concentration
  - Regardless of conc, drug gone after 5-7 $T_{1/2}$’s
  - A proportionality constant, dependent on Cl & Vd

\[
T_{1/2} = \frac{0.693 \times Vd}{Cl}
\]

• **Clearance / Elimination:** related to volume and $T_{1/2}$ of drug

\[
T_{1/2} = \frac{0.693}{K_e} \quad K_e = \frac{Cl}{Vd} \quad Cl = K_e \times Vd
\]

AB is a 42 yo WM being treated for TB with SM 1000mg (~13 mg/kg) IV QM-F.

Other meds: RIF/EMB/PZA
- AB has a h/o CHF, ESLD, and DM.
- Wt = 75 kg, Ht = 65 in.
- Labs: BUN = 15, SCr = 1.1
- SM MIC = 8 mcg/ml
- Serum SM concs reveal:
  - Calculated Cmax = 22 mcg/ml  \( (nl=35-45\ mcg/ml) \)
  - Serum \( T_{1/2} \) = 5.2 hrs  \( (nl\ SM\ T_{1/2} = 2-3\ hrs) \)
What is the most likely cause of AB's serum SM concentrations and PK parameters being not quite normal?

<table>
<thead>
<tr>
<th>A</th>
<th>Renal dysfunction</th>
</tr>
</thead>
<tbody>
<tr>
<td>B</td>
<td>Large volume of distribution</td>
</tr>
<tr>
<td>C</td>
<td>Reduced absorption of the streptomycin</td>
</tr>
<tr>
<td>D</td>
<td>Drug interaction affecting metabolism of SM</td>
</tr>
</tbody>
</table>
Use of PK / PD Principles in TB Therapy
PK/ PD Response Parameters

• **Time > MIC**
  - More frequent dosing to maintain time above the MIC
  - INH, Ethionamide

• **AUC > MIC**

• **Cmax / MIC**
  - Concentration-dependent
  - Best given as large (usually daily) doses
  - Aim for ratio of at least 10-12
  - AMG’s, FQ’s, Rifamycins
PD: Response Parameters

Cmax = 9 mcg/ml
MIC = 3 mcg/ml

Cmax/MIC = 3

T > MIC = 8h

AUC (mcg * h/ml)
Ethionamide

T > MIC = ~ 4h
INH Concs. by Acetylator status

SLOW = t½ 3.35 hr, AUC 54.9 mcg*hr/mL

Int. = t½ 1.56 hr, AUC 35.7 mcg*hr/mL

FAST = t½ 1 hr, AUC 25.0 mcg*hr/mL

Pharmaco-KINETICS

Prescribed Dosing Regimen

Drug at Site of Action

Drug Effects

• Dosing & med errors
• Absorption
• Tissue & body fluid mass and volume
• Drug interactions
• Elimination
• Drug metabolism
• Adherence

Pharmaco-DYNAMICS

• Genetic factors
• Drug interactions
• Tolerance
• Pt factors
• Drug receptor status
• Effect of drug COMBOS

PD: Impact of PK Mismatch

• PK Mismatch
  – Short $T_{1/2}$ drug + long $T_{1/2}$ drug $\rightarrow$ Resistance or Failure

• Reports in TB
  – Strong relationship between low INH and therapeutic failure/relapse in QW INH/RPT\(^1\)
  – No effect of mismatch\(^2\): INH and *rifampin*
  – Important in HIV co-infection\(^3, 4\)

**PK Mismatch → PD Response:**
Low INH with Rifampin & Rifapentine

<table>
<thead>
<tr>
<th>PK Param</th>
<th>BIW I/Rif Failure/Relapse (n=16)</th>
<th>Cure (n=33)</th>
<th>PValue</th>
<th>QW I/Rpt Failure/relapse (n=22)</th>
<th>Cure (n=49)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>INH</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Med AUC</td>
<td>43.3</td>
<td>48.4</td>
<td>0.65</td>
<td>36.0</td>
<td>55.9</td>
<td>0.0005</td>
</tr>
<tr>
<td>Med Cmax</td>
<td>11.9</td>
<td>10.2</td>
<td>0.9</td>
<td>11.1</td>
<td>11.9</td>
<td>0.08</td>
</tr>
<tr>
<td>Med T1/2</td>
<td>2.1</td>
<td>2.3</td>
<td>0.42</td>
<td>1.4</td>
<td>2.4</td>
<td>0.02</td>
</tr>
<tr>
<td><strong>Rifamycin</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Med AUC</td>
<td>46.1</td>
<td>50.5</td>
<td>0.23</td>
<td>211</td>
<td>196</td>
<td>0.47</td>
</tr>
<tr>
<td>Med Cmax</td>
<td>8.3</td>
<td>7.7</td>
<td>0.96</td>
<td>12.3</td>
<td>12.2</td>
<td>0.31</td>
</tr>
<tr>
<td>Med T1/2</td>
<td>2.2</td>
<td>3.4</td>
<td>0.11</td>
<td>14.6</td>
<td>16.8</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Reduced Concentrations in HIV+

EFFECT: RFB & INH AUC in HIV+ → ARR Failures / Relapse

ID (TB): Usual PK/PD Response Parameters

• **Time > MIC**
  - More frequent dosing to maintain time above the MIC
  - *INH*, Ethionamide

• **AUC > MIC**
  - FQ’s, Rifamycins

• **Cmax / MIC**
  - Concentration-dependent
  - Best given as large (daily, intermittent) doses
  - *Aim for* Cmax to MIC ratio of at least 10-12 (AMG’s)
  - AMG’s, FQ’s, Rifamycins
PD: Response Parameters

Cmax = 9 mcg/ml
MIC = 3 mcg/ml

Cmax/MIC = 3

T > MIC = 8h

AUC (mcg * h/ml)
Streptomycin

Cmax = 64 mcg/ml
MIC = 8 mcg/ml

Cmax/MIC = 8
**Rifampin 600 mg in Humans**

Cumulative % Culture Negative

<table>
<thead>
<tr>
<th>Month</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>$H_{300}R_{600}Z_2S_2$ QD</td>
<td>38</td>
<td>77</td>
<td>97</td>
</tr>
<tr>
<td>$H_{300}R_{600}Z_2E_2$ QD</td>
<td>35</td>
<td>77</td>
<td>99</td>
</tr>
</tbody>
</table>

Other doses:
- S 750mg, Z 35mg/kg, E 25mg/kg, R 450 mg if <50kg

Rifampin _1200mg_ in Humans

Cumulative % Culture Negative

<table>
<thead>
<tr>
<th>Month</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>H₉₀₀R₁₂₀₀S₂  QD</td>
<td>72</td>
<td>94</td>
<td>98</td>
</tr>
<tr>
<td>H₉₀₀R₁₂₀₀S₂  QOD*</td>
<td>70</td>
<td>93</td>
<td>100</td>
</tr>
</tbody>
</table>

Other doses: S 1000 mg QD* both regimens

## Rifampin 600mg vs 1200mg

### Cumulative % Culture Negative

<table>
<thead>
<tr>
<th>Month</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>$H_{300}R_{600}Z_2S_2$</td>
<td>38</td>
<td>77</td>
<td>97</td>
</tr>
<tr>
<td>$H_{900}R_{1200}S_2$</td>
<td>72</td>
<td>94</td>
<td>98</td>
</tr>
</tbody>
</table>

Other doses: S 750mg in first, 1000 mg QD in second

**Note:** RIF dose response also seen with INH 300mg + RIF 450mg, 600mg, or 750mg QD (Long et al)

Rifampin 1200mg

• Flu-like syndrome: NOT reported by Kreis et al
  • More related to *intermittent* therapy

• May be best to **optimize** current regimens

Pt Case: AB Dose Optimization

- **Recall** that AB had an SM Cmax of 22 mcg/ml and an SM MIC of 8 mcg/ml. AB also had an extended serum T1/2 of 5.2 hrs.
We are concerned about the effectiveness of this SM dose because of which dosing principle?

| The Time > MIC is not optimal | A |
| The Cmax / MIC is not optimal | B |
| The AUC > MIC is not optimal | C |
Use of Therapeutic Drug Monitoring (TDM) in TB
Therapeutic Drug Monitoring (TDM)*

GOAL: Optimization of therapy for individual pt:
• Maximize efficacy
  and/or
• Minimize toxicity

Use with other clinical data

Most valuable when
• Wide intersubject variation
• Therapeutic concs ≈ toxic concs
• Serum concs → surrogate for concs at site of action

TDM: What it’s really about

- NOT necessarily “normal” ranges
- Rather, individualized goals for each pt.
- **Goals** should consider:
  - Efficacy needs
  - Toxicity acceptance

- Once drug is chosen:
  - Determine desired conc.
  - Try to achieve!

- “Therapeutic” concentrations vary by patient

TDM with TB Drugs

May be more important than adherence(??)¹

- Meta-analysis: PK variability to single drug associated with failure & acquired resistance
- Need at least 60% non-adherence to impact outcomes

Useful for²⁻⁴

- Slow to respond to treatment
- Drug-resistant TB
- Risk of drug-drug interactions
- Concurrent disease (HIV, DM, Hep/renal dysfunction)

PD: Drug tolerance

Aminoglycoside Toxicity

• AK, SM, KM Regimens in TB and MAC:
  – 12-15 mg/kg IV 5x/wk → Cmax = 35-45 mcg/ml
  – 22-25 mg/kg IV TIW → Cmax = 65-80 mcg/ml

• Dose or serum concentrations did not predict:
  – Hearing loss
  – Vestibular toxicity
  – Nephrotoxicity

• Conclusions
  – Older pts → minimize duration
  – Larger pts → ok to go >1000mg

**TDM: “How to” guide**

<table>
<thead>
<tr>
<th>Drug</th>
<th>1-2 hr post-dose</th>
<th>6 hr post-dose</th>
<th>10 hr post-dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>INH</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Rifampin</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Ethambutol</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>X</td>
<td></td>
<td>X (ideally)</td>
</tr>
<tr>
<td>AK, SM, CM, KM*</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>(*or 30 min /p infusion)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Levo$ &amp; Moxi</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Cycloserine</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>PAS</td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Ethionamide</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

- Two or more time-points ideal (better PK info)
  - If can only do one, check the Cmax (“peak”; first one)
- **Consult an expert**
- Don’t be afraid of the info! *Dose “max” is not necessarily the max in your patient*
- $ New data for AUC / Population-based model: 0 and 4 hrs
Back to AB:

Recall:

• AB is a 42 yo WM being treated for TB with:
  – SM 1000mg (~13 mg/kg) IV QM-F,
  – RIF 600 mg po QD,
  – EMB 800 mg po QD,
  – PZA 1000 mg po QD.

AB has a h/o CHF, ESLD and DM.
Which other med(s) might we be most concerned about not being optimized in AB (and why)?

<table>
<thead>
<tr>
<th>Rifampin</th>
<th>A</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rifampin and PZA</td>
<td>B</td>
</tr>
<tr>
<td>Rifampin and Ethambutol</td>
<td>C</td>
</tr>
</tbody>
</table>
Rifampin serum concs. reveal \((nl = 8-24 \text{ mcg/ml})\):

- 2 hr: 6 mcg/ml
- 6 hr: 3 mcg/ml
Without doing PK calculations, what might be a better new RIF dose (and why)?

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>RIF 600 mg IV QD</td>
</tr>
<tr>
<td>B</td>
<td>RIF 600 mg PO BID</td>
</tr>
<tr>
<td>C</td>
<td>RIF 900 mg PO QD</td>
</tr>
</tbody>
</table>
Conclusions

• Overview of PK/PD
  – PK – time course ADME; PD - effect at site
  – Therapeutic Drug Monitoring (TDM)

• PK / PD in TB
  – INH – time-dependent
  – RIF, AMGs – concentration dependent
  – PK mismatch important, especially with INH and long half-life rifamycins (RFB and RPT)

• Use of TDM in TB
  – Important in TB tx
  – Offers individualized tx
    • Efficacy / Toxicity
    • Drug Interactions / Concurrent clinical problems
With an understanding of PK/PD and TDM, let’s aim to make TB treatment \textit{NOT} “the same as it ever was.”

Questions?
References

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- Perlman DC et al for the ACTG 309 Team. The clinical pharmacokinetics of rifampin and ethambutol in HIV-infected persons with TB. Clin Infect Dis 2005; 41:1638-47.