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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Same as it ever was…
Yeah, the twister comes
Here comes the twister
Same as it ever was…

- *Once in a Lifetime*, Talking Heads¹

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

Pharmaco-DYNAMICS

- Genetic factors
- Drug interactions
- Tolerance
- Drug receptor status

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

\[ C_{in} \]  \[ C_{out} \]

Organ of Elim’n (Kidney, Liver)

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

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

PK Case – AB – *PK Parameter*

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 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  \( (nl=35-45 \text{ mcg/ml}) \)
  - Serum \( T_{1/2} \) = 5.2 hrs  \( (nl \text{ SM } T_{1/2} = 2-3 \text{ hrs}) \)
Pt Case AB Question

What is the most likely cause of AB’s serum SM concentrations and PK parameters being not quite normal?

a. Renal dysfunction  
b. Large volume of distribution  
c. Reduced absorption of the streptomycin  
d. Drug interaction affecting metabolism of SM
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
Cmax = 9 mcg/ml
MIC = 3 mcg/ml

Cmax/MIC = 3

T > MIC = 8h

AUC (mcg * h/ml)
Ethionamide

$C_{\text{max}}$

$T > \text{MIC} = \sim 4h$

$0 \quad 4 \quad 8 \quad 10 \quad 12$

$0 \quad 0.5 \quad 1.0 \quad 1.5 \quad 2.0 \quad 2.5$
INH Concs. by Acetylator status

- SLOW = $t_{1/2}$ 3.35 hr, AUC 54.9 mcg*hr/mL
- Int. = $t_{1/2}$ 1.56 hr, AUC 35.7 mcg*hr/mL
- FAST = $t_{1/2}$ 1 hr, AUC 25.0 mcg*hr/mL

Pharmaco-KINETICS

Prescribed Dosing Regimen

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

Pharmaco-DYNAMICS

Drug at Site of Action

- Genetic factors
- Drug interactions
- Tolerance
- Pt factors
- Drug receptor status

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
  – 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></td>
<td>36.0</td>
<td>55.9</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

- N=5; Acquired rifamycin resistance (ARR)
- N=90; no ARR failure or relapse

ID (TB): Usual 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 (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)

AUC > MIC
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&lt;sub&gt;300&lt;/sub&gt;R&lt;sub&gt;600&lt;/sub&gt; Z&lt;sub&gt;2&lt;/sub&gt;S&lt;sub&gt;2&lt;/sub&gt; QD</td>
<td>38</td>
<td>77</td>
<td>97</td>
</tr>
<tr>
<td>H&lt;sub&gt;300&lt;/sub&gt;R&lt;sub&gt;600&lt;/sub&gt; Z&lt;sub&gt;2&lt;/sub&gt;E&lt;sub&gt;2&lt;/sub&gt; 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>H$<em>{900}$ R$</em>{1200}$ S$_2$ QD</td>
<td>72</td>
<td>94</td>
<td>98</td>
</tr>
<tr>
<td>H$<em>{900}$ R$</em>{1200}$ S$_2$ 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>H&lt;sub&gt;300&lt;/sub&gt;R&lt;sub&gt;600&lt;/sub&gt;</th>
<th>Z&lt;sub&gt;2&lt;/sub&gt;</th>
<th>S&lt;sub&gt;2&lt;/sub&gt;</th>
<th>QD</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>38</td>
<td>77</td>
<td>97</td>
</tr>
<tr>
<td></td>
<td>H&lt;sub&gt;900&lt;/sub&gt;R&lt;sub&gt;1200&lt;/sub&gt;</td>
<td></td>
<td>S&lt;sub&gt;2&lt;/sub&gt;</td>
<td>QD</td>
<td></td>
<td>72</td>
<td>94</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?
  a) The Time > MIC is not optimal
  b) The Cmax / MIC is not optimal
  c) The AUC > MIC is not optimal
Use of Therapeutic Drug Monitoring (TDM) in TB
Therapeutic Drug Monitoring (TDM)*

*aka “Clinical Pharmacokinetics”

**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 adherence¹

- 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>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></td>
<td></td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>AK, SM, CM, KM* (*or 30 min /p infusion)</td>
<td>X</td>
<td>X</td>
<td>X (ideally)</td>
</tr>
<tr>
<td>Levo &amp; Moxi</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Cycloserine</td>
<td></td>
<td>X</td>
<td></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*
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 and DM.
AB - Regimen Questions:

Which other med(s) might we be most concerned about not being optimized in AB (and why)?

a) Rifampin
b) Rifampin and PZA
c) Rifampin and Ethambutol
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)?

a) RIF 600 mg IV QD
b) RIF 600 mg PO BID
c) RIF 900 mg PO QD
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 *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.