Therapeutic Drug Monitoring in the Management of Tuberculosis

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Disclosures

• No disclosures
Objectives

• Review the time/concentration profile of IV and orally administered TB medications

• Review common pharmacokinetic concepts in relation to understanding/interpreting serum drug levels

• Define appropriate draw times for serum level assessment and anticipated serum level ranges for individual TB medications

• Describe case scenarios to highlight the interpretation of serum levels and consequent dose adjustment in TB management
Abbreviations

- RIF = Rifampin
- INH = Isoniazid
- EMB = Ethambutol
- PZA = Pyrazinamide
- CS = Cysloserine
- AMK = Amikacin
- PAS = para-aminosalicylic acid
- TB = Tuberculosis
- TDM = Therapeutic Drug Monitoring
- PK = Pharmacokinetic
- PD = Pharmacodynamic
- DOT = Daily observed Therapy
- SOB = Shortness of breath
- AUC = Area Under the Curve
- AG = aminoglycoside
- ART = Antiretroviral therapy
- Cmax = Maximum concentration (peak)
- Cmin = Minimum concentration (trough)
- RCT = Randomized Controlled Trial
- Log = logarithm
- h = hours
- M = male
- F = Female
- DM = Diabetes mellitus
- HIV = Human immunodeficiency virus
- Pt = patient
Why do drug levels in TB?

- Efficacy Target
- Minimize toxicity
- Compliance measure
- Confirm absorption
- Assess degree/presence of drug interaction
Concerns with level assessment

• Lack of published RCT outcome data
• PK-PD goals not conclusively elucidated for humans
• Small # of patients with low levels on standard doses have still had positive outcomes
Practicality of TDM

• Standard doses of TB medications typically yield positive results
• Standard doses yield predictable ‘standard’ concentrations
• Helps establish a threshold which we would not wish to drop below
• Confirms absorption of medications
Bottom line

• TDM gives objective, patient specific information to the clinician

• This can enhance informed decisions regarding the dose of medications to treat tuberculosis
Contribution to patient outcome

- Drug levels
- Condition of patient
- Disease Extent
- Organism Susceptibility
- Bacteriologic response
- Clinical response

TB Patient outcome

Mayo Clinic Center for Tuberculosis
What drug levels represent?
Serum levels = surrogate marker

Concentration (ug/ml)

$C_{\text{max}}$

Time (h)
Pharmacokinetic relationships

Concentration (ug/ml) vs. Time (h)

- **C_{max}**: Peak concentration
- **t_{1/2}**: Half-life
- **T_{max}**: Time to peak concentration
- **C_{min}**: Minimum concentration

Graph shows the typical profile of a drug's concentration over time, highlighting key points such as the peak concentration and the time it takes to reach this peak. The graph also indicates the duration of the drug's effect and its clearance rate.
Rate of elimination = Clearance x Concentration
Pharmacokinetic/Pharmacodynamic relationships

- $C_{\text{max}}$
- $C_{\text{max}}/\text{MIC}$
- AUC/MIC
- MIC
- T>MIC
- Sub-MIC
- PAE
- $T_{\text{max}}$

Concentration (ug/ml)

Time (h)

0 1 2 4 8 12 24
Time-Concentration Curves

- Intermittent infusion
- Continuous infusion
- Extended infusion

Concentration vs. Time

MIC
Pharmacodynamic targets

• $C_{\text{max}}$:MIC
  • Rifamycins
  • FQ
  • AG

• AUC/MIC
  • PZA
  • FQ
  • Linezolid

• $T > \text{MIC}$
  • Linezolid
Which draw times/levels to use for TDM?
Typically use Peak ($C_{\text{max}}$) draws

- Reasons for 2 hour peak draw
  - Troughs often below assay detection limit
  - Absorption information
  - $T_{\text{max}}$ is close to 2 hours for most tuberculosis medications
Example of peak assessment
2h and 6h post dose levels
Benefits of a 2h and 6h draw level

- 2\textsuperscript{nd} level info on rate and completeness of absorption
- Clearance
- Distinguish between delayed absorption and malabsorption
Limitations of a 2h and 6h approach

- Still only 2 time points
## Pharmacokinetic parameters

<table>
<thead>
<tr>
<th>Drug</th>
<th>Normal adult dose</th>
<th>Normal $C_{\text{max}}$ ($\mu$g/mL)</th>
<th>Normal $T_{\text{max}}$ (h)</th>
<th>Normal $t_{1/2}$ (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td>300 mg daily</td>
<td>3–6</td>
<td>0.75–2</td>
<td>Polymorphic: fast: 1.5; slow: 4</td>
</tr>
<tr>
<td></td>
<td>900 mg biw</td>
<td>9–15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rifampin</td>
<td>600 mg daily</td>
<td>8–24</td>
<td>2</td>
<td>2–3</td>
</tr>
<tr>
<td>Rifabutin</td>
<td>300 mg daily</td>
<td>0.45–0.90(^a)</td>
<td>3–4</td>
<td>25–36</td>
</tr>
<tr>
<td>Rifapentine</td>
<td>600 mg daily(^b)</td>
<td>8–30</td>
<td>5</td>
<td>15</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>25–35 mg/kg daily</td>
<td>20–60</td>
<td>1–2</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>50 mg/kg biw</td>
<td>60–90</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethambutol</td>
<td>25 mg/kg daily</td>
<td>2–6</td>
<td>2–3</td>
<td>Biphasic: 2–4, then 12–14</td>
</tr>
<tr>
<td></td>
<td>50 mg/kg biw</td>
<td>4–12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cycloserine</td>
<td>250–500 mg daily or biw</td>
<td>20–35</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>Ethionamide</td>
<td>250–500 mg daily or biw</td>
<td>2–5</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Streptomycin/</td>
<td>15 mg/kg daily</td>
<td>35–45(^c)</td>
<td>0.5–1.5 h IM dose or</td>
<td>3</td>
</tr>
<tr>
<td>kanamycin/ amikacin</td>
<td></td>
<td></td>
<td>calculated to the end of IV infusion</td>
<td></td>
</tr>
<tr>
<td>PAS granules</td>
<td>4,000 mg bid</td>
<td>20–60</td>
<td>4–8</td>
<td>1</td>
</tr>
<tr>
<td>Levoflaxacin</td>
<td>500–1,000 mg daily</td>
<td>8–13</td>
<td>1–2</td>
<td>9</td>
</tr>
<tr>
<td>Moxiflaxacin</td>
<td>400 mg daily</td>
<td>3–5</td>
<td>1–2</td>
<td>7</td>
</tr>
<tr>
<td>Linezolid</td>
<td>600–300 mg</td>
<td>12–26</td>
<td>1.5</td>
<td>5–6</td>
</tr>
<tr>
<td></td>
<td>1–2 times daily</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clofazimine</td>
<td>100 mg daily</td>
<td>0.5–2.0</td>
<td>2–7</td>
<td>Biphasic: several days, then many weeks</td>
</tr>
</tbody>
</table>

Alsultan, Peloquin; Drugs (2014) 74:839–854
Where can I send levels?

• National Jewish Advanced Diagnostics lab
  • [http://www.nationaljewish.org/professionals/clinical-services/diagnostics/adx/Overview](http://www.nationaljewish.org/professionals/clinical-services/diagnostics/adx/Overview)

• University of FL- ID pharmacokinetics lab
  • [http://idpl.pharmacy.ufl.edu/](http://idpl.pharmacy.ufl.edu/)
Examples and cases
Case 1
Case 1

- 33 yo M (78kg) diagnosed with non-cavitary pulmonary tuberculosis. Normal renal/hepatic fxn. No comorbidities. Started meds (below), setup for receiving DOT, clinically responding well.
  - RIF 600mg
  - INH 300mg
  - EMB 1200mg
  - PZA 1000mg
Case 1

• When would you like to perform TDM and on which drug(s)?
  • A. After next dose, all medications
  • B. After 5\textsuperscript{th} dose of medications, all medications
  • C. After 2 weeks of therapy, only RIF and INH
  • D. TDM is not necessary for this patient
When to draw levels?

• Draw levels at steady state
  • Drug input over the dosing period = drug eliminated over the dosing period
  • $C_{\text{max}}$ and $C_{\text{min}}$ consistent

• Usually takes ~5 half-lives
When to perform TDM

• Slow or lack of response
• Clinically worsening
• Complicated disease
  • Bilateral pulmonary disease, cavitary disease
• Tuberculosis relapse
• Presence of potential/known drug interactions
• Comorbid conditions
  • DM
  • HIV
• Renal failure/Hepatic compromise
  • No good marker for hepatic function
  • Both can have n/v issues contributing to malabsorption
  • Issues with malabsorption and delayed clearance
• Drug-resistant TB
TDM in everyone?

- Debatable!

- Low drug levels:
  - correlate with lower response rates
  - increased potential for drug resistance

- Interpatient variable kinetics
  - Some patients on standard doses will have lower levels
  - Early identification helpful

- Pharmacoeconomic analyses lacking
Case 1 Take Home Points

• When taking therapeutic drug levels, take them at steady state
  • Steady state attainment at 5 half-lives
  • When half-life is 4 - 5hrs, pt is at steady state within a day

• Not all patients will require TDM
Case 2
Case 2

- 55 yo (52 kg) Hmong female with cavitary tuberculosis. Started on INH 250mg, RIF 600mg, PZA 1000mg, and EMB 800mg daily. Dc’d from hospital after one week and daily DOT initiated. After initial clinical improvement, patient notes return of SOB, fevers, and increased cough. Pt is very aggravated with DOT and not happy with public health visits to her home.
Case 2

- TDM (after 3 weeks) on her TB medications show the following:
  - 2h post dose levels:
    - PZA – below the lower limit of detection
    - EMB – below the lower limit of detection
    - INH – below the lower limit of detection
    - RIF – below the lower limit of detection
  - Scr 0.6, Lytes WNL, Hgb 12.3, AST 24/ALT 18, Bilirubin T/D: 0.1/0.2, WBC 8.8, Uric acid 2.4mg/dl (WNL)
Case 2

• How would you like to manage going forward?
  • A. Increase drug doses with later recheck of drug levels 2h and 6h after dose, as patient likely has malabsorption
  • B. Continue current doses and recheck levels, ensuring blood is drawn, prepared and shipped according to appropriate storage methods
  • C. Advise patient to withhold food for 2h prior to daily dose administration
  • D. Consider hospital admission for supervised dose administration
TDM collection requirements

• Follow specific instructions from receiving laboratory
• Samples generally placed on ice
• Prompt centrifugation, followed by freezing serum as soon as possible
  • INH/Ethionamide not stable at room temp
Affect of food

• Food can delay and reduce INH and RIF absorption
  • High fat meals decrease INH peak levels by ~50%

• Administration on an empty stomach preferable if possible

• Small low fat meal reasonable if gastrointestinal intolerance for medication tolerability
PZA

- Great marker for compliance
- Most reliably absorbed TB medication
- Long half-life of ~9h
- Measurable serum levels at 24h
- Reliably increases serum uric acid in patients
Case 2 take home points

• Ensure adequate specimen collection/handling for TDM
• Food can affect absorption of INH/Rifampin, though food can mitigate GI upset
• PZA and uric acid are great markers for compliance
Case 3
Case 3

• 18 yo (71kg) M with cavitary pulmonary TB. Rifampin resistance was discovered via the GeneXpert assay and patient was a contact of a known rifampin mono-resistant case. Pt has normal renal/hepatic function and has clinically improved on his regimen.
  • Current regimen: INH 300mg, EMB 1200mg, PZA 1000mg, Moxifloxacin 400mg, and Amikacin 900mg daily.
Case 3

• Would you perform TDM on this patient?
• A. No, patient is clinically improving
• B. Yes, levels at end of infusion for Amikacin
• C. Yes, 2h and 6h levels for all agents
• D. Check PZA level at 2h. If within normal limits, no other levels need be drawn
One-compartment model

Input → Body → Eliminated drug

k
Two-compartment model

Input

Blood

Distribution sites

k

Eliminated drug
Aminoglycoside level timing

We can use a one compartment model and equations when levels are taken after drug distribution phase.

Taking levels during the distribution phase will inappropriately affect our calculations and misrepresent our extrapolations.
Aminoglycosides and level timing

• Aminoglycosides levels need to be drawn after the end of the distribution phase
  • Recommend drawing a level 2 hours and 6 hours after the end of infusion
  • Ensures levels are artificially inflated
  • Allows the use of one-compartment kinetic equations

• Calculate a back-extrapolated peak (based on a one-compartment model)

• Base dose adjustments on calculated peak

• Goal calculated peak is **35-45mcg/ml**
Case 3 drug levels return

INH 300mg, EMB 1200mg, PZA 1000mg, Moxifloxacin 400mg, Amikacin 900mg daily

• INH:
  • 2h level (4mcg/ml); 6h level (1mcg/ml)

• EMB:
  • 2h level (3mcg/ml); 6h level (1.4mcg/ml)

• PZA:
  • 2h level (33.4mcg/ml); 6h level (24.6mcg/ml)

• Moxifloxacin:
  • 2h level (1.8 mcg/ml); 6h level (1.1mcg/ml)

• Amikacin:
  • 2h level (14mcg/ml); 6h level (3.8 mcg/ml)
Useful pharmacokinetic equations

Formula to describe the elimination rate constant $k$

- $C_1 = C_2 \times e^{(k \times \Delta t)}$

Assumptions

- One-compartment kinetic model
- Levels drawn in the post-absorptive, post-distributive phase of elimination
Useful pharmacokinetic equations

Need to solve for $k$

- $C_1 = C_2 \times e^{(k \times \Delta t)}$
- $k = \frac{\ln (C1/C2)}{\Delta t}$

- $k$ is the elimination rate constant
- $k$ gives us the half life and the ‘slope’ of our graph
- We need $k$ to find the back-extrapolated peak value
- **Half life = 0.693/k**
  - If $k = 0.331$ h$^{-1}$, then half life = 3h
Finding the elimination rate constant

Need to solve for $k$

- $C_1 = C_2 \times e^{(k \times \Delta t)}$

- $k = \frac{\ln (C_1/C_2)}{\Delta t}$

- $k = \frac{\ln (14/3.8)}{4h} = 0.326 \text{ h}^{-1}$

- Half life = $0.693/k = 2.1 \text{ h}$

- We can now use $k$ to find the back-extrapolated peak value
Calculating our peak

Use k to solve for our peak

- \( C_0 = \text{calculated Cmax} \)
  - End of infusion

- \( C_0 = C_1 \times e^{(k \times t)} \)

- \( C_0 = 14 \times e^{(0.326 \times 2)} \)

- \( 26.9 \text{ mcg/ml} \)
  - Goal is 35-45mcg/ml
Case 3 drug levels return

INH 300mg, EMB 1200mg, PZA 1000mg, Moxifloxacin 400mg, Amikacin 900mg daily.

- **INH:**
  - 2h level (4mcg/ml); 6h level (1mcg/ml)

- **EMB:**
  - 2h level (3mcg/ml); 6h level (1.4mcg/ml)

- **PZA:**
  - 2h level (33.4mcg/ml); 6h level (24.6mcg/ml)

- **Moxifloxacin:**
  - 2h level (1.8 mcg/ml); 6h level (1.1mcg/ml)

- **Amikacin:**
  - 2h level (14mcg/ml); 6h level (3.8 mcg/ml)
  - Back-extrapolated peak: 26.9mcg/ml
Case 3

• How would you adjust doses?

• A. Moxifloxacin 400mg q48h, increase Amikacin to 2gm daily

• B. Moxifloxacin 600-800mg daily and Amikacin 1300mg daily

• C. Same dose Moxifloxacin (400mg daily) and increase Amikacin 1gm daily

• D. No changes to either medication
Case 3 take home points

- Patients with drug resistance should have TDM performed
- We assess AG levels as a standard to ensure PK-PD goal efficacy/toxicity
- AG peak values are calculated with 2 post-distribution levels: Goal level is 35 - 45mcg/ml
- AG levels at end of infusion are artificially inflated
- Peak:MIC ratio with FQ optimizes bacterial kill
Case 4
Case 4

- 47 yo (63 kg) M from Philippines with MDR non-cavitary pulmonary tuberculosis. Rif/INH/AMK resistant. His regimen is:
  - PZA 1500mg daily
  - EMB 1200mg daily
  - Moxifloxacin 400mg daily
  - CS 250mg qam/500qpm
  - PAS granules 4gm twice daily
  - Linezolid 600mg daily

- Pt is clinically improving without any hepatic/renal disease. No comorbidities.

- Following provider orders 2h drug levels
Case 4 - 2 hour drug levels return

- PZA 1500mg daily
  - 2h level (38.2 mcg/ml)

- EMB 1200mg daily
  - 2h level (3.7 mcg/ml)

- Moxifloxacin 400mg daily
  - 2h level (4.2 mcg/ml)

- CS 250mg qam/500qpm
  - Levels taken after 500mg dose
  - 2h level (24 mcg/ml)

- PAS granules 4gm twice daily
  - 2h level (6.2 mcg/ml)

- Linezolid
  - 2h level (21.4 mcg/ml)
Case 4

• How would you like to adjust the PAS dose?
  • A. Increase to 4gm three times daily
  • B. Increase to 8gm twice daily
  • C. Increase to 6gm (1.5 packets) twice daily
  • D. Check a 4-6h level of PAS to better assess.
Case 4 - take home points

• PAS granules are enteric coated and delayed release
  • $T_{\text{max}}$ is between 4 and 6 hours

• PAS tablets (not in US), $T_{\text{max}}$ is ~2h

• PAS $C_{\text{max}}$ 20-60 mcg/mL
Case 5
Case 5

• 31 yo F (74kg) with bilateral non-cavitary pulmonary TB. She has INH and EMB resistance. Normal renal/hepatic function. No comorbidities. Her regimen is:

  • Rifampin 600mg daily
  • PZA 1500mg daily
  • Moxifloxacin 400mg daily
Case 5

• Her 2h and 6h drug levels return as follows:

  • **Rifampin 600mg daily**
    • 2h level (6.8 mcg/ml); 6h level (1.7 mcg/ml)

  • **PZA 1500mg daily**
    • 2h level (31.2mcg/ml); 6h level (19.6mcg/ml)

  • **Moxifloxacin 400mg daily**
    • 2h level (2.2 mcg/ml); 6h level (1.4 mcg/ml)
Case 5

• How would you adjust doses?
  • A. No dose adjustments necessary
  • B. Consider increasing Rifampin to 900mg daily and Moxifloxacin to 600-800mg daily
  • C. Consider increasing Rifampin to 900mg daily and continue Moxifloxacin 400mg daily
  • D. Consider increasing PZA to 3gm, reduce Rifampin to 450mg, and increase Moxifloxacin to 600mg daily
Case 5 take home points

• FQ and Rifampin have concentration dependent effects
• Goal Rifampin Cmax is >8mcg/ml
• Goal Moxifloxacin Cmax is 3-5mcg/ml
• Moxifloxacin levels can be reduced ~30% when combined with Rifampin, dose adjustments are usually warranted
• Watch for high FQ doses and QT prolongation
Case 6

• 44 yo (69kg) HIV positive male (CD4 583/VL UD on ART with Raltegravir and Truvada) who is on Rifabutin 300mg, INH 300mg, EMB 1200mg, and PZA 1500mg daily for non-cavitary pulmonary TB. His primary physician contacted ID regarding his returned drug levels:

  • Rifabutin 0.48 mcg/ml
  • INH: undetectable
  • EMB: 1.2mcg/ml
  • PZA: 18 mcg/ml
Case 6

• What dosing recommendations would you recommend?

- A. Rifabutin- no change; INH 600mg daily, EMB 1600mg daily, PZA 2000mg daily
- B. Rifabutin- no change; INH 400mg daily, EMB 1600mg daily, PZA 2000mg daily
- C. Rifabutin- 450mg daily; INH 400mg daily, EMB 1600mg daily, PZA 2000mg daily
- D. No changes. Verify draw time relative to dose administration. Verify compliance and redraw levels at 2h and 6h post oral doses.
Case 6 take home points

• Levels mean little without knowing compliance level and draw time relative to dose administration

• Interpreting levels without knowing dose administration history and draw times is inappropriate
Summary

• TDM is a useful tool in management of TB

• Knowing how to use this tool will aid with optimizing efficacy/minimizing toxicity
  • Appropriate level interpretation
  • PK-PD goals
Closing

• “No model is correct. However, some are useful.”

• “Although it may seem a paradox. All exact science is dominated by approximation.”
  • -B. Russell
Questions?
Plasma concentration vs time profile

**Single intravenous bolus dose**

**Single oral dose**
Plasma concentration vs time profile

- **Constant rate infusion**
- **Intermittent infusion**
- **Interval PO dosing**