Treatment of Tuberculosis

“Therapeutic Drug Monitoring”

2nd European Advanced Course in Clinical Tuberculosis

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Overview

• Background & definitions
• Why & How
• Clinical case presentation
• Tools for TDM
• TDM in programmatic TB treatment
Clinical Pharmacokinetics is about all the factors that determine variability in the concentration of the drug in time.

Therapeutic Drug Monitoring is about treatment optimization based on the drug concentration and clinical characteristics and condition of the patient.
Therapeutic Window

Drug concentration

Effect

Toxicity
Does drug concentration matter?

“1% of tuberculosis patients with perfect adherence would still develop MDR-tuberculosis due to pharmacokinetic variability alone”

“Low rifampin and isoniazid peak and AUC concentrations preceded all cases of acquired drug resistance”.

“Poor outcomes were observed in patients with at least 1 drug concentration below the target (OR = 14.14).”

Srivastava JID 2012, Pasipanodya JID 2013
INH concentration related failure

- Thirteen randomized studies
  - 1631 rapid acetylators
  - 1751 slow acetylators
- Rapid acetylators were more likely than slow acetylators to have:
  - microbiological failure (RR, 2.0; CI, 1.5–2.7)
  - acquired drug resistance (RR, 2.0; CI, 1.1–3.4)
  - relapse (RR, 1.3; CI, .9–2.0)

Higher failure rates were encountered even in drug regimens comprising >3 antibiotics.
How do we optimize treatment using TDM?
Drug concentration => Effect?

• Correlation:
  – drug concentration and therapeutic response
  – drug concentration and toxicity

• Inter and intra patient PK variability
PK/PD parameters

Absorption / Distribution / Clearance

- **C<sub>max</sub>**
- **C<sub>min</sub>**
- **AUC**
- **AUC/MIC ratio**
- **C<sub>max</sub>/MIC ratio**
- **T > MIC**

<table>
<thead>
<tr>
<th>Time post dose</th>
<th>Serum concentration</th>
</tr>
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<tbody>
<tr>
<td>0</td>
<td></td>
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<tr>
<td>24h</td>
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Moxifloxacin

- **Target** → AUC/MIC ratio > 100 [1-3]

\[ \log_{10} \text{CFU/lung} \]

\[ fAUC/MIC \]

Time, days

\[ R^2 = 0.94 \]

Moxifloxacin

7-fold diff. in AUC
8-fold diff in MIC (0.125-1 mg/L)
AUC/MIC ratio: 82 (21–320)
Moxifloxacin; influence of disease?

- Female, 42 yrs from Indonesia with MDR-TB
  - 34kg
  - HIV positive
- Routine TDM:
  - Day 7 (●)
  - After 7 weeks (○)
TB-HIV “RIF”

- Male, 27 yrs from Russia
- HIV positive
- DST: normal sensitive
- Standard treatment
  - HRZE
- TDM for HIV drugs
  - also TB drugs
Case (continued)

![Graph showing rifampin concentration over time post dosage with two lines: one for PO 600mg and one for IV 600mg.]

- rifampin concentration (mg/L) on the y-axis
- time post dosage (h) on the x-axis
- Two lines: one for PO 600mg and one for IV 600mg
TB-HIV patients

N=2:

“In addition to the use of DOT to ensure compliance, we advocate routine screening of antimycobacterial-drug levels in HIV-infected patients with tuberculosis, particularly those with advanced HIV disease.”

N=287

“We believe this is an important area for continued investigation, particularly correlations of low body weight with both adverse drug reactions and therapeutic drug levels of MDR-TB treatments.”

Routine care today?

Patel et al NEJM 1995; Farley PlosOne 2011
Which blood sample to take from my patient?

Rifampin Peak ≠ C2
Methods of blood sampling

- Classical: trough/peak
- Full PK curve
- Optimized:
  - limited sampling
Plasma and/or dried blood sample

- **Plasma**
  - Venous access
  - Samples often instable
  - ‘Relative simple’ equipement

- **Dried blood spot**
  - Convenient sampling
  - Sample stability
  - Whole blood instead of plasma
  - Advanced equipement
Dried blood spot sampling; clean
Dried blood spot sampling; prick
Dried blood spot sampling; wipe
Dried blood spot; card
Dried blood spot sampling; blood
Dried blood spot sampling; spot
Dried blood spot sampling
Dried blood spot cards

Vu et al J Chrom B 2011
TDM in programmatic TB treatment

- Populations at risk for low drug exposure
- Patients failing to respond to treatment
- M/XDR-TB
- Use limited sampling strategy
- Use DBS sampling
To summarize:

- **Patient Characteristics**
- **Response to treatment**
- **WHO treatment**
- **Protocol for Programmatic TDM**
- **Drug concentration (AUC)**
- **Drug susceptibility (MIC)**