Pharmacology and Pharmacokinetics of TB Drugs, Part II

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Where Does TB Drug PK Data Come From?

“Well, you never will believe where those Keebler cookies come from they’re made by little guys in a hollow tree ...

Disclaimer – I have no stock in this Co.
Where Does TB Drug PK Data Come From?

Considerable pharmacokinetic data were generated by:

Gordon Ellard
Gianni Acocella
Ludo Verbist

among others...
Where Does TB Drug PK Data Come From?

Data were compiled from all available sources (both healthy volunteers and TB patients) by:

Mack Holdiness Clin Pharmacokinet. 1984; 9 (6) : 511 - 44
Charles Peloquin (1991 and later)
Global Alliance for TB Drug Development
Handbook of Anti-Tuberculosis Agents 2008

among others...
CHAPTER 2
ANTITUBERCULOSIS DRUGS: PHARMACOKINETICS
Charles A. Peloquin, Pharm.D.


191 references
Where Does TB Drug PK Data Come From?

Only after the ranges were published did we complete a series of Phase I studies in healthy volunteers validating the ranges previously established (published 1997 and later).

So, the ranges commonly used in the TB literature actually reflect what you might expect to see in your TB patients, and what they should be able to tolerate.
PK issue: Drug Interactions

Gene: CYP 3A4          Enzyme: P450 IIIA4

Inducers:

rifampin, rifapentine, rifabutin,
carbamazepine, phenytoin,

efavirenz, nevirapine

St. John’s Wort
PK: Drug Interactions

Gene : CYP 3A4          Enzyme: P450 IIIA4

**Inhibitors:**
clarithromycin, erythromycin,
fluconazole, itraconazole, ketoconazole,
amprenavir, indinavir, nelfinavir,
ritonavir, saquinavir, delavirdine
Most available data comes from:

1. small numbers of healthy volunteers, studied under controlled conditions, receiving only the 2 interacting drugs

2. case reports with multiple uncontrolled variables and multiple other drugs
PK: Drug Interactions

Data from 2-way interactions are helpful, but you need to consider:

1. single dose versus steady-state
2. variability in the data
3. outliers (high or low response)
4. data may not provide any insight into 3-way or 4-way interactions
Effect of rifamycins on serum concentrations (AUC) of protease inhibitors

<table>
<thead>
<tr>
<th>PI</th>
<th>Rifabutin (Δ%)</th>
<th>Rifampin (Δ%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saquinavir</td>
<td>↓ 46%</td>
<td>↓ 80%</td>
</tr>
<tr>
<td>Ritonavir</td>
<td>NR</td>
<td>↓ 35%</td>
</tr>
<tr>
<td>Indinavir</td>
<td>↓ 24%</td>
<td>↓ 90%</td>
</tr>
<tr>
<td>Nelfinavir</td>
<td>↓ 0-23%</td>
<td>↓ 82%</td>
</tr>
<tr>
<td>Amprenavir</td>
<td>↓ 14%</td>
<td>↓ 81%</td>
</tr>
<tr>
<td>Lopinavir/ritonavir</td>
<td>No effect</td>
<td>↓ 75%</td>
</tr>
<tr>
<td>Atazanavir</td>
<td>No effect</td>
<td>not done</td>
</tr>
</tbody>
</table>
### Effect of protease inhibitors on serum concentrations (AUC) of rifamycins

<table>
<thead>
<tr>
<th>PI</th>
<th>Rifabutin</th>
<th>Rifampin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saquinavir</td>
<td>↑ 45%</td>
<td>NR</td>
</tr>
<tr>
<td>Ritonavir</td>
<td>↑ 400%</td>
<td>unchanged</td>
</tr>
<tr>
<td>Indinavir</td>
<td>↑ 270%</td>
<td>NR</td>
</tr>
<tr>
<td>Nelfinavir</td>
<td>↑ 200%</td>
<td>NR</td>
</tr>
<tr>
<td>Amprenavir</td>
<td>↑ 400%</td>
<td>NR</td>
</tr>
<tr>
<td>Lopinavir/ritonavir</td>
<td>↑ 300%</td>
<td>NR</td>
</tr>
<tr>
<td>Atazanavir</td>
<td>↑ 250%</td>
<td>NR</td>
</tr>
</tbody>
</table>
The drug **must access** the organism and bind to a target to produce an inhibitory or lethal effect.

**Access** requires absorption and delivery by the blood to the site of infection.

By Analogy:
**Gravity** – not just a good idea - it’s the law
Malabsorption, or lack of blood flow to the site of infection, lead to treatment failures and to the selection of resistance.

The question: Standardized treatment for everyone, and if they don’t respond, continue the same tx,

Or

See why this is happening, adapt, and overcome.
Slow responses to TB treatment are common, as shown on the next slide.

While many of these slow responses are due to treatment interruptions (adverse drug reactions, patients leaving treatment programs, etc.), in our experience, a substantial portion of these are due to poor drug absorption.
Therapeutic Drug Monitoring (TDM)

aims to promote optimum drug treatment by maintaining serum drug concentrations within a "normal range," or preferably a "therapeutic range"

How can we apply this?
Completion of TB Therapy, United States, 1993 – 2010*

* Updated as of June 10, 2013. Data available through 2010 only.

Note: Includes persons alive at diagnosis, with initial drug regimen of one or more drugs prescribed, who did not die during therapy. Excludes persons with initial isolate rifampin resistant, or patient with meningeal disease, or pediatric patient (aged <15) with miliary disease or positive blood culture.
Completion of TB Therapy, United States, 1993 – 2010*

• Updated as of June 10, 2013.
• Data available through 2010 only.

Note: Includes persons alive at diagnosis, with initial drug regimen of one or more drugs prescribed, who did not die during therapy.

Excludes: rifampin resistant TB, meningeal disease, or pediatric patients (aged <15) with miliary disease or positive blood culture.
TB Treatment Is Guideline-Driven

The standard claim is that TB can be treated with a 6-month regimen that has roughly 98% success, followed by about 3% relapses, for about a 95% overall cure.
Completion of TB Therapy, United States, 1993 – 2010*

• So, what percentage of US TB patients complete the 6-month regimen in 6 months?
<table>
<thead>
<tr>
<th>Treatment month</th>
<th>Completed therapy ≤1 year indicated**</th>
<th>% of those COT-eligible</th>
</tr>
</thead>
<tbody>
<tr>
<td>COT within 6 months or less</td>
<td>1709</td>
<td>18.0%</td>
</tr>
<tr>
<td>COT by 7 months</td>
<td>4257</td>
<td>44.9%</td>
</tr>
<tr>
<td>COT by 8 months</td>
<td>5003</td>
<td>52.8%</td>
</tr>
<tr>
<td>COT by 9 months</td>
<td>5956</td>
<td>62.8%</td>
</tr>
<tr>
<td>COT by 10 months</td>
<td>7426</td>
<td>78.3%</td>
</tr>
<tr>
<td>COT by 11 months</td>
<td>7865</td>
<td>83.0%</td>
</tr>
<tr>
<td>COT by 12 months</td>
<td>8354</td>
<td>88.1%</td>
</tr>
</tbody>
</table>
So what?

Remember, this is supposed to be a 6-month "short-course" therapy.

If it takes 12 to 18 months, it is no longer "short-course" therapy...

and you pay for every month.  

$12 / 6 = 2$
So what?

“In theory, there is no difference between theory and practice. In practice, there is.”

Yogi Berra
The average weight of the patients, predominantly male, in the BMRC Hong Kong and East Africa trials was 48 kg.

\[
\frac{600 \text{ mg}}{48 \text{ kg}} = 12.5 \text{ mg/kg}
\]

\[
\frac{600 \text{ mg}}{90 \text{ kg}} = 6.7 \text{ mg/kg}
\]

For many patients, we give a lot less drug than was studied originally …
And this is what it looks like …

Full: 600 mg in Original patients

Not Full: 600 mg in Current patients

48 kg

96 kg
Kind of like putting 10 gallons of gas in each of these vehicles ...
PD: Sterilizing Activity of Rifampin

Jayaram et al, AAC (2003); 47:2118

Mean value after 600 mg oral dose
most useful when there is a direct relationship between serum concentrations and therapeutic response, and when serum concentrations serve as a surrogate for drug concentrations at the site of action.
most important when there is a narrow range of concentrations that are effective and safe, and when toxicity or lack of effectiveness puts the patient at great risk
in conjunction with other clinical data, allows for an assessment of the patient's status, and for timely therapeutic interventions
Standardized doses tell your PK “seat” is located somewhere in this the stadium.
TDM shows you precisely which PK “seat” you have.
Jelliffe R.

Goal-oriented, model-based drug regimens: setting individualized goals for each patient.

Roger Jelliffe’s Key Points:

“Therapeutic” concentrations vary by patient.

Once a drug is chosen, a goal should be set for the desired serum concentrations.

This goal should be achieved with the greatest precision possible.
Roger Jelliffe’s Key Points:

In other words, if you are relying on drugs to **cure** the patient, you may as well give the **right amount** to EACH patient.
TDM with Oral TB Drugs

Two hour post dose blood draws generally capture the “peak” concentration.

Six hour post dose blood draws generally separate delayed absorption from malabsorption.

Rifampin Plasma Concentrations

- NIH A
- NIH B
- AACTG
- Vols

Time (hour) vs Concentration (mcg/ml)
The decision to use TDM is the same as the decision to check a CBC with diff., or the decision to get a CT or MRI. None of these guarantees the outcome of Tx. However, all of these inform the clinician prior to making clinical decisions.
Role for TDM

TDM allows you to **individualize** therapy.

TDM allows you to **optimize** the pharmacodynamically-linked variable [typically Cmax or AUC].
Role for TDM

TDM may allow you to **shorten** treatment, or to **avoid** concentration-related toxicities.

TDM allows you to **unravel** complicated **multi-drug** interactions.
So what is the big idea, anyway?

In the end, **knowing** is better than **guessing**.
Thanks

• Thanks to Eric Nuermberger, MD and William Burman, MD for providing several slides

• The IDP Lab Team:
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