Pharmacokinetics (PK) and Therapeutic Drug Monitoring (TDM)

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How Do Antibiotics Work?

For every drug with a proven mechanism of action, this action involves the drug entering the organism, binding to a target, and producing an inhibitory or lethal effect.

How Do Antibiotics Work?

For every drug given orally or parenterally, the only way for the drug to reach the bug is through the bloodstream.
**How Do Antibiotics Work?**

If it ain’t in the blood,  
it ain’t in the bug.  
Therefore, pharmacokinetics matters...

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**Pharmacokinetics (PK)**

The study of the movement of drugs  
through the body.  
“What the body does to the drug.”  
Most commonly based on the study of  
serum concentrations in relation to dose.

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**Moxifloxacin concentrations, TBRU Study**

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Moxifloxacin concentrations, TBRU Study

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.


Patterns of Absorption with Oral Drugs
**Patterns of Absorption with Oral TB Drugs**

Normal patterns of absorption may be associated with normal or low concentrations.

Delayed patterns of absorption may indicate low concentrations, or may indicate that the “peak” occurred between the 2 draws.

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**Patterns of Absorption with Oral TB Drugs**

Malabsorption indicates the need to increase the dose.

The absolute size of the dose is **meaningless** when one has serum concentration data to support dosing decisions.

The patient is letting you know what they **need**.

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**Patterns of Absorption with Oral TB Drugs**

Example of the patient letting you know what they **need**:

If the “usual” dose of warfarin is 5 mg, yet at 2 weeks the INR is 1.2, most clinicians will increase the dose, because that is what is needed!

The situation is the same with TB drugs!
Another example of the patient letting you know what they need:
If the “usual” dose of propranolol is 40 mg, yet at 4 weeks the blood pressure is unchanged, most clinicians will increase the dose, because that is what is needed!

The situation is the same with TB drugs!!

The “maximum” doses in the guidelines are NOT supported by clinical data. They are based upon the “perception of what might be safest.”

Nearly all clinical trials used the same doses!

It would be better to call the “maximum” doses “usual” doses, since that is what they are.

The “maximum” doses in the guidelines also typically are the “minimum” doses.

The probability that one and only one dose (example: rifampin 600 mg) is both the correct maximum and the correct minimum dose for the nearly entire human population on the planet is approximately ZERO.
Patterns of Absorption with Oral TB Drugs

The REAL maximum dose is the dose that produces the desired clinical effect at an acceptable level of toxicity.

For a gravely ill patient, more toxicity is acceptable, given the alternative.

Therapeutic Drug Monitoring (TDM)

<table>
<thead>
<tr>
<th>Jelliffe R.</th>
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<tbody>
<tr>
<td>Goal-oriented, model-based drug regimens: setting individualized goals for each patient.</td>
</tr>
</tbody>
</table>

TDM

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.
TDM

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

TDM

- in conjunction with other clinical data, allows for an assessment of the patient's status, and for timely therapeutic interventions

TDM

- The decision to use TDM is the same as the decision to get a CDC with differential or a chemistry panel or a CT scan.
- Will the data allow you to make a clinical decision?
- If yes, you should get the data.
Q. How high of a dose can you give?
A. As high as necessary

Actual examples:

INH 900 mg daily, RIF 2100 mg daily because most of the doses were ending up in the patient’s stool.

Otherwise, if you keep doing what you have been doing, you will keep getting what you have been getting.

TDM

DiPiro JT, Spruill WJ, Wade WE, Blouin RA, Pruemer JM
Concepts in Clinical Pharmacokinetics, 5th Ed.
American Society of Health-System Pharmacists 2010.

Moxifloxacin concentrations, TBRU Study
PK: Plasma Elimination Half-Life

$t_{1/2}$ is defined as the time for concentrations (in plasma) to decline by 50%.

After 7 $t_{1/2}$'s, nearly all of the drug is gone, regardless of the starting concentration.

$t_{1/2}$ is independent of dose and concentration.

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INH Slow Acetylator over 24 h

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PK: Calculating half-life

<table>
<thead>
<tr>
<th>Two Sample Infusion</th>
<th></th>
<th></th>
<th>Ln Conc</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Conc</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>26.30</td>
<td>2.00</td>
<td></td>
<td>3.27</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9.40</td>
<td>6.00</td>
<td></td>
<td>2.24</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Slope</th>
<th>Intercept</th>
<th>$k_e$</th>
<th>$t_{1/2}$</th>
<th>$C_{max}$</th>
<th>$C_{max}$ intercept</th>
</tr>
</thead>
<tbody>
<tr>
<td>-0.26</td>
<td>3.78</td>
<td>0.257</td>
<td>2.69</td>
<td>43.99</td>
<td>43.99</td>
</tr>
</tbody>
</table>
PK: Calculating half-life

\[ \text{Ln Conc vs Time} \]

PK: Clearance

t½ is inversely proportional to the clearance of a drug (Cl).

Clearance can be thought of as the size of the drain in the bathtub.

A big drain will empty the tub faster.

PK: Clearance

**Clearance organs:**

**Kidneys**: especially for water soluble drugs
- creatinine clearance might predict

**Liver**: metabolize drugs to make water soluble
- AST, ALT usually do not predict
PK: Volume of Distribution

$t_{1/2}$ is directly proportional to the volume of distribution ($V$).

$V$ can be viewed as the size of the bathtub. Big tubs take a longer time to drain.

$t_{1/2}$ is viewed as a proportionality constant, dependent upon $Cl$ and $V$.

PK: Volume of Distribution

Large volumes of distribution typically reflect drug penetration into tissues which return the drug to the plasma space only slowly.

Drug molecules inside of tissues are unavailable to the organs of clearance.

Pharmacokinetics: Modeling

Why model data?

Allows for simulation of future scenarios: You can see “What if...?” on your computer screen before you see it in your patient.

This is especially good if you don’t like what you see on your computer screen.
Pharmacokinetic Evaluation of Rifabutin in Combination with Lopinavir-Ritonavir in Patients with HIV Infection and Active Tuberculosis

Catherine Boulanger, Elena Hollender, Karen Farrell, Jeff Stambaugh, Diane Maasen, David Ashkin, Stephen Symes, Luis A. Espinoza, Rafael O. Rivero, Jenny J. Graham, and Charles A. Peloquin

Clinical Infectious Diseases 2009; 49:1305–11

Pharmacodynamics (PD)

the study of the relationships between drug concentrations and responses

“What the drug does to the body.”

Methods

- *in vitro* models
- animal models
- human clinical trials with dose escalation

Probability (%)

Drug Concentration (µg/ml)

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td>100</td>
</tr>
<tr>
<td>20</td>
<td>30</td>
</tr>
<tr>
<td>40</td>
<td></td>
</tr>
</tbody>
</table>

Evans, 1986
Cmax = 9 mcg / ml
MIC = 3 mcg / ml
Cmax / MIC = 3
T > MIC = 8 h
AUC ( mcg * h / ml )
PD: Sterilizing Activity of Rifampin

Mean value after 600 mg oral dose

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

PD: Response Data

Association between Acquired Rifamycin Resistance and the Pharmacokinetics of Rifabutin and Isoniazid among Patients with HIV and TB [Study 23A].


Clinical Infectious Diseases 2005; 40: 1481 - 1491.
Lesser rifabutin AUC with ARR versus cure

<table>
<thead>
<tr>
<th>Group</th>
<th>No.</th>
<th>Dose mg/kg Med (IQC)</th>
<th>AUC&lt;sub&gt;0-24&lt;/sub&gt; Med (IQC)</th>
<th>P- Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARR</td>
<td>6</td>
<td>4.5 (3.5 - 5.7)</td>
<td>5.1 (2.0 - 3.6)</td>
<td>0.04</td>
</tr>
<tr>
<td>CURE</td>
<td>82</td>
<td>4.6 (4.2 - 6.2)</td>
<td>5.1 (4.0 - 7.0)</td>
<td></td>
</tr>
</tbody>
</table>

* P for RBT AUC ARR vs. cure, Mann-Whitney

Table 4. Results of multivariate logistic regression analysis, adjusted for CD4+ cell count, of TB treatment failure or relapse with acquired rifamycin-resistant mycobacteria.

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR (95% CI)</th>
<th>P by the Wald test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low rifabutin AUC 0–24</td>
<td>23 (2–279)</td>
<td>0.01</td>
</tr>
<tr>
<td>CD4+ cell count</td>
<td>1.04 (1.00–1.08)</td>
<td>0.07</td>
</tr>
</tbody>
</table>


Pharmacokinetic Evaluation of Rifabutin in Combination with Lopinavir–Ritonavir in Patients with HIV Infection and Active Tuberculosis

Catherine Boulanger, Elena Hollender, Karen Farrell, Jerry Jean Stambaugh, Diane Maassen, David Ashkin, Stephen Symes, Luis A. Espinoza, Rafael O. Rivero, Jenny J. Graham, and Charles A. Peloquin

Clinical Infectious Diseases 2009; 49:1305–11
Rifabutin and LPV/r in HIV+ TB Patients

- Low RBN concentrations were common
- 1 patient developed ARR during the course of the PK study (very small study, 10% ARR)
- desacetyl–RBN activity against TB is questionable

Interactions: Rifabutin

- Many dosage recommendations are based on healthy volunteer data only.
- Dosing recommendations assume that all patients are the median healthy volunteer.
- MIC data are not routinely collected in clinical practice to identify patients who might need more RBN for a more resistant TB isolate.
- Unlike RIF regimens, RBN failures are ARR
Rifabutin in HIV positive patients

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 guarantee the outcome of Tx.

However, all of these inform the clinician prior to making clinical decisions.

Also, the decision to use TDM is the decision to change the dose if indicated by the data.

TDM for TB Drugs

INH, RIF, PZA, EMB

Cost of TDM: $80 per test / $140 per pair
2 time points x 4 drugs = 8 tests
4 x $140 / pair = $560
plus, hassle, shipping costs, unfamiliarity...
Cost of Treatment: $10,000 over 6 months

Cost of Treatment for ARR: Initial $10,000
plus an additional $30,000 over 18 more months
Total: $40,000 and 2 years (plus secondary cases)

[Now, $560 does not look so bad…]

### Therapeutic Drug Monitoring (TDM)

TDM allows you to individualize therapy

TDM allows you to optimize the pharmacodynamically-linked variable

### 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