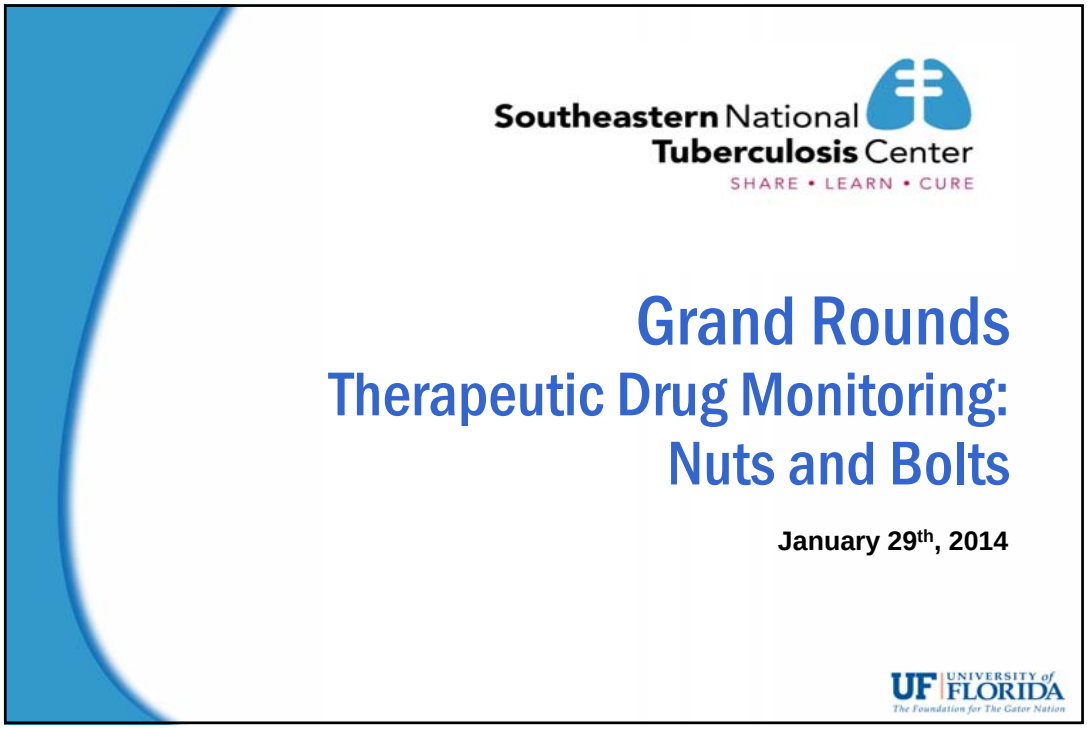


Therapeutic Drug Monitoring (TDM): Nuts and Bolts

Charles A. Peloquin, Pharm. D.
Professor, and Director
Infectious Disease Pharmacokinetics Laboratory
College of Pharmacy and
The Emerging Pathogens Institute
University of Florida

So what is the big idea, anyway ?

In general, there are two ways to dose a drug :

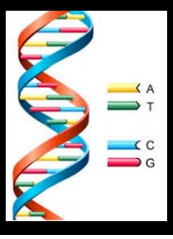
Guessing (also know as one size fits all)

and

Knowing (also know as personalized medicine)

So what is the big idea, anyway ?

In the most modern sense, personalized medicine refers to individualizing drug therapy based on a patient's unique genetic information.



So what is the big idea, anyway ?

In the old school sense, personalized medicine refers to seeing how much drug actually made it into the patient's blood, and seeing how long it hangs out there.

So what is the big idea, anyway ?

Given my age, I'm "old school."

Why ?

" You can observe a lot by just watching."

Yogi Berra

TB Treatment Is Guideline - Driven

TABLE 3. Doses* of antituberculosis drugs for adults and children†

Drug	Preparation	Adults/children	Doses			
			Daily	11×/wk	2×/wk	3×/wk
First-line drugs						
Isoniazid	Tablets (50 mg, 100 mg, 300 mg); elixir (50 mg/5 ml); aqueous solution (100 mg/ml) for intravenous or intramuscular injection	Adults (max.) Children (max.)	5 mg/kg (300 mg) 10–15 mg/kg (300 mg)	15 mg/kg (900 mg) —	15 mg/kg (900 mg) 20–30 mg/kg (900 mg)	15 mg/kg (900 mg) —
Rifampin	Capsule (150 mg, 300 mg); powder may be suspended for oral administration; aqueous solution for intravenous injection	Adults‡ (max.) Children (max.)	10 mg/kg (600 mg) 10–20 mg/kg (600 mg)	— —	10 mg/kg (600 mg) 10–20 mg/kg (600 mg)	10 mg/kg (600 mg) —
Pyrazinamide	Tablet (500 mg, scored)	Adults Children (max.)	See Table 4 15–30 mg/kg (2.0 g)	— —	See Table 4 50 mg/kg (2 g)	See Table 4 —
Ethambutol	Tablet (100 mg, 400 mg)	Adults Children§ (max.)	See Table 5 15–20 mg/kg daily (1.0 g)	— —	See Table 5 50 mg/kg (2.5 g)	See Table 5 —

TB Treatment Is Guideline - Driven

Guidelines are very <u>important</u>, and

very <u>useful</u>. They are the right place to <u>start</u>.

What we will talk about is " <u>and then</u>…"

TB Treatment Is Guideline - Driven

The implicit assumption within the guidelines is that if you can get the patient to take the drugs, they will be cured.

Increasingly, that assumption is being challenged…

Multidrug – resistant tuberculosis not due to noncompliance but to between - patient pharmacokinetic variability.

Srivastava S, Pasipanodya JG, Meek C, Leff R, Gumbo T.

J Infect Dis 2011 ; 204 : 1951 - 9.

Experiments using an *in vitro* hollow fiber model of TB.

Integrating drug concentrations and minimum inhibitory concentrations with Bayesian - dose optimisation for multidrug - resistant tuberculosis.

Srivastava S, Gumbo T.

Eur Respir J 2014 ; 43 : 312- 3.

Explains an approach to handling clinical data.

Therapeutic drug monitoring in the treatment of tuberculosis.

Peloquin CA.

Drugs 2002 ; 62 : 2169 – 83.

Explains an approach to handling clinical data.

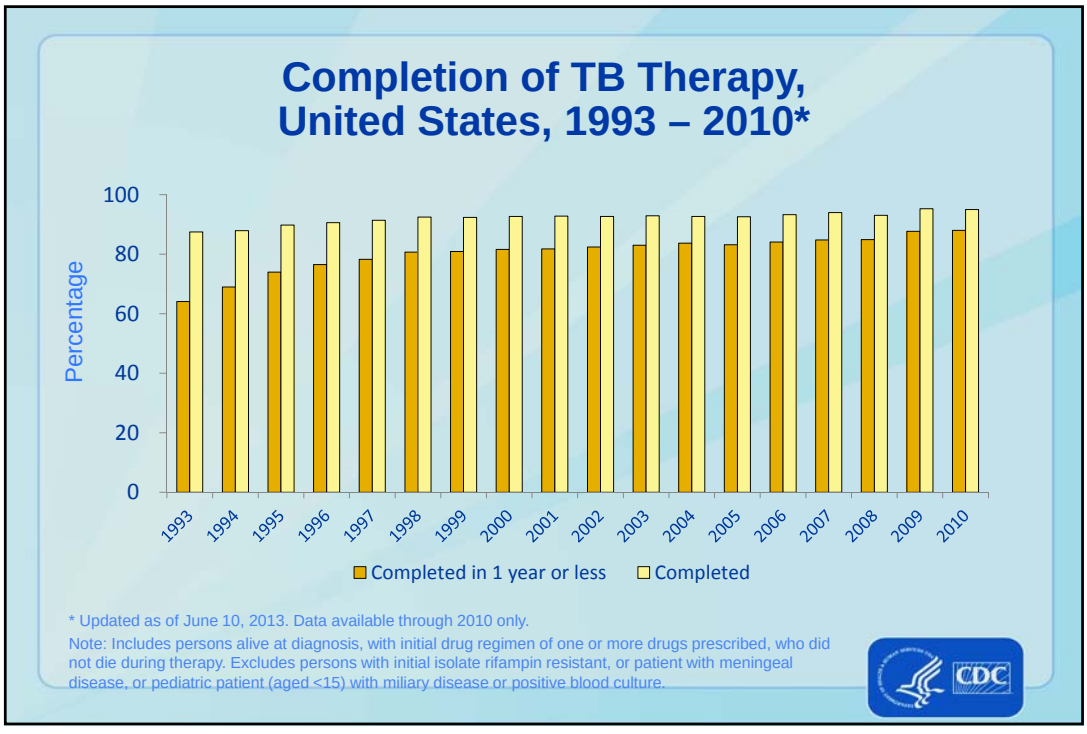
Standardized doses tell your PK "seat" is located somewhere in this the stadium.

Therapeutic Drug Monitoring shows you precisely which PK "seat" you have.

Role for Therapeutic drug monitoring

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.



So what is the big idea, anyway ?

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

If it takes 12 to 18 months,

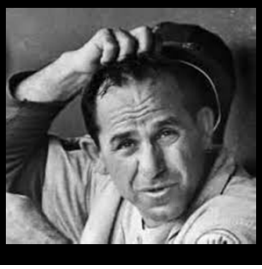
it is no longer "short – course" therapy.

18 / 6 = 3

So what is the big idea, anyway ?

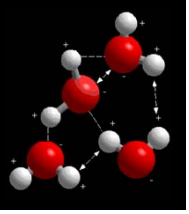
" In theory, there is no difference between theory and practice. In practice, there is."

Yogi Berra



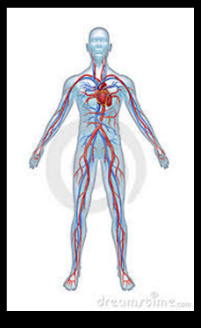
How Do Antibiotics Work ?

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 blood stream.



How Do Antibiotics Work ?

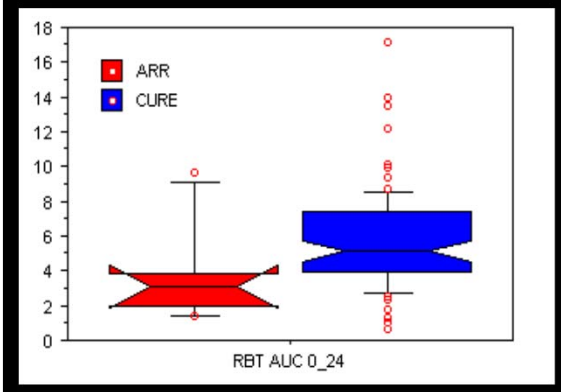
If it ain't in the blood,

it ain't in the bug.

Therefore, pharmacokinetics matters…

" Hey pal, you missed ! "

Example : Lower rifabutin AUC with Acquired Rifamycin Resistance (ARR) versus cure



Group	No.	Dose mg/ kg Med (IQC)	AUC_{0-24} Med (IQC)	P-Value*
ARR	6	4.6 (3.5 - 5.7)	3.1 (2.0 - 3.8)	
CURE	82	4.8 (4.2 – 6.2)	5.1 (4.0 - 7.4)	0.04

- P for RBT AUC ARR vs. cure, Mann-Whitney
- ARR Odds ratio for RBN AUC = 23
- ARR Odds ratio for CD4 count = 1.04

Clinical Infectious Diseases 2005; 40: 1481 - 1491.

How Do Antibiotics Work ?

The moral of the story…

when you take your shots…

don't miss.

Limited Choices

Aminosalicylate sodium (PAS)	
Capreomycin	Cycloserine
Ethionamide	Ethambutol
Isoniazid	Pyrazinamide
Rifampin or	Rifapentine
Streptomycin	Bedaquiline NEW!

Quinolones, Linezolid,
and other un-approved drugs

…and you use 4 at a time…

Trouble ahead, trouble behind…

Malabsorption, or lack of blood flow to the site of infection, lead to <u>treatment failures</u> and to the <u>selection of resistance</u>.

The <u>failure to identify and correct the problem</u> reduces the choices at your disposal, while the patient remains <u>uncured</u> and under your care.

"Casey Jones you better watch your speed…"

Trouble ahead, trouble behind…

<u>The Standardized Approach</u>: continue the same treatment and don't look for trouble.

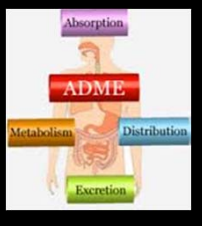
or

<u>The Alternative Approach</u>: investigate why this is happening, adapt, and overcome.

Pharmacokinetics (PK)

The study of the movement of drugs through the body.

Most commonly based on the study of serum concentrations in relation to dose.



Applied Pharmacokinetics

Using pharmacokinetics in the clinical setting to achieve the desired serum concentrations.

Also known as therapeutic drug monitoring, or TDM.

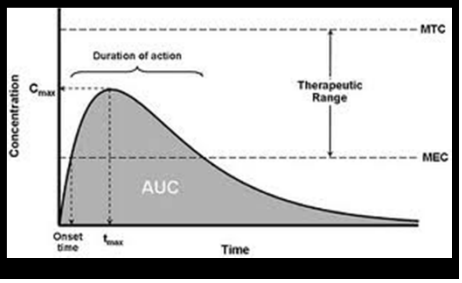
Therapeutic Drug Monitoring (TDM)

aims to promote optimum drug treatment

by maintaining serum drug concentrations

within a "normal range," or preferably

a "therapeutic range"



TDM

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

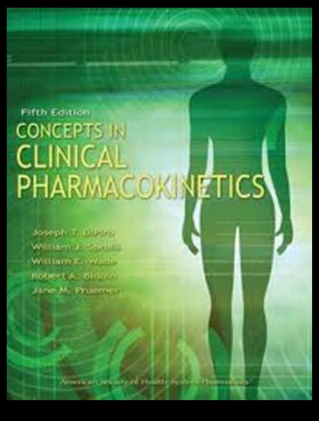
at the site of action

TDM

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

TDM

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



TDM

Jelliffe R.

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

Ther Drug Monit **2000**; 22: 325 – 329.

TDM

Roger Jelliffe's Key Points:

" Therapeutic " concentrations vary by patient

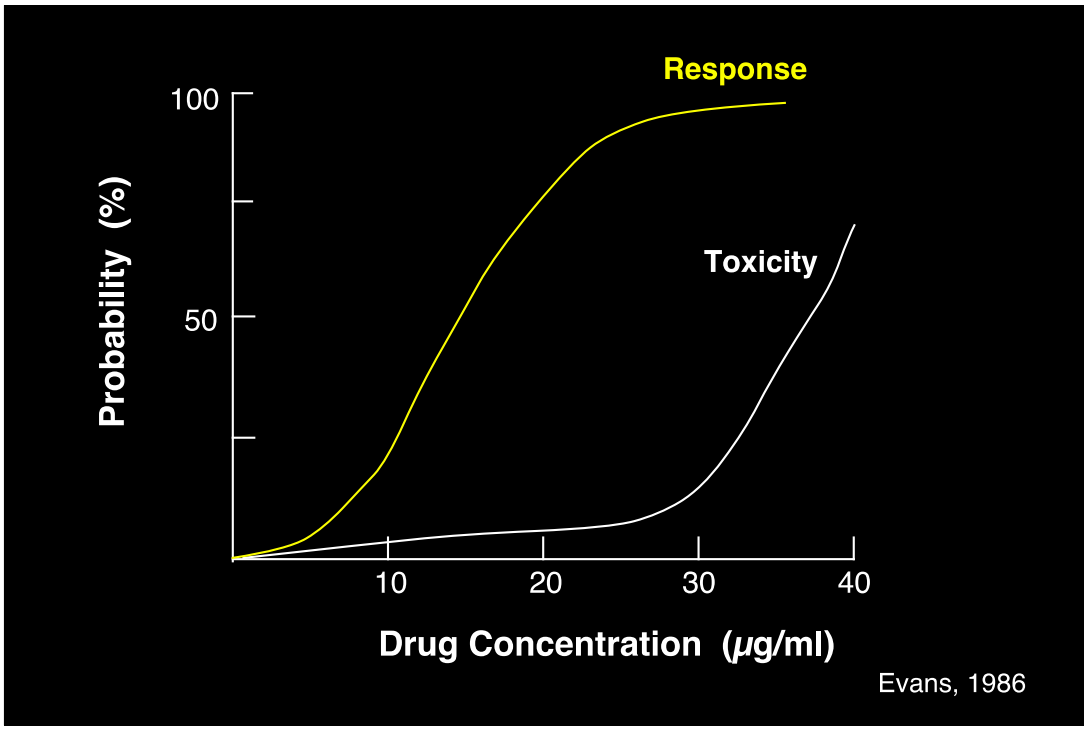
Once a drug is chosen, a goal should be set for the desired serum concentrations.

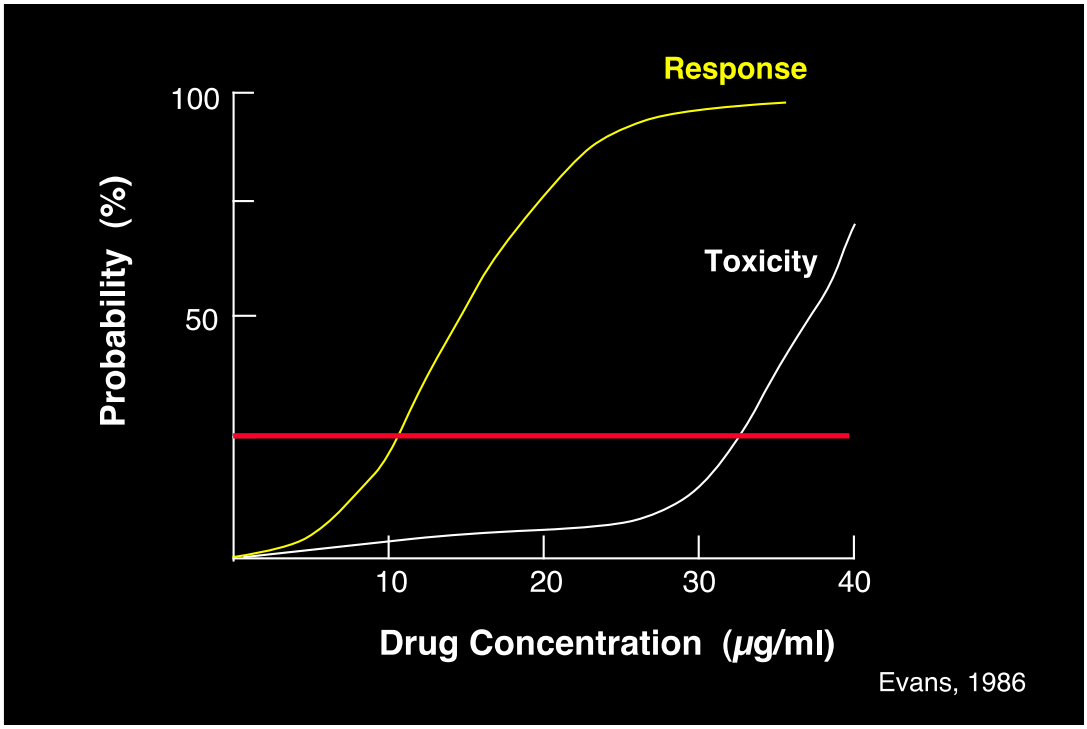
This goal should be achieved with the greatest precision possible.

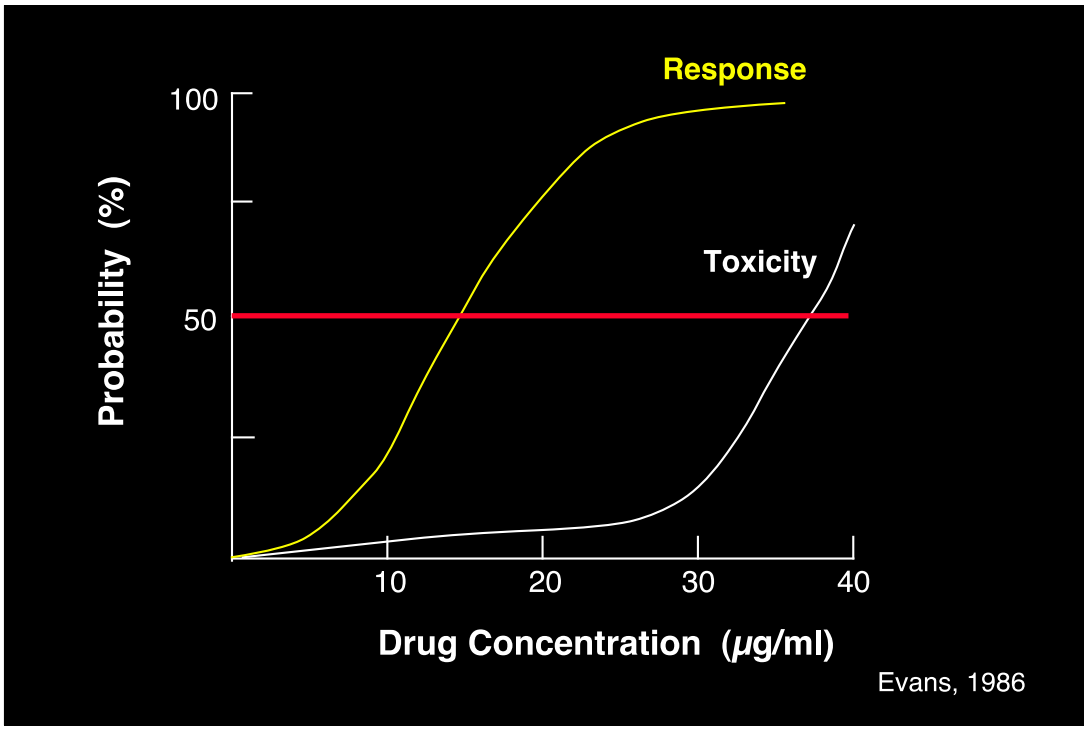
TDM

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.



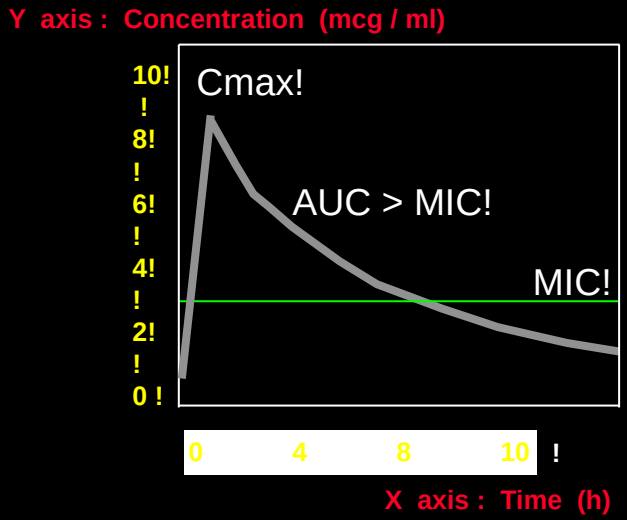

Response
Toxicity
100
50
Probability (%)
10
20
30
40
Drug Concentration (μg/ml)
Evans, 1986


Response
Toxicity
100
50
Probability (%)
10
20
30
40
Drug Concentration (μg/ml)
Evans, 1986

ID: Usual PK - PD Response Parameters

- **Cmax / MIC**
- **Time > MIC**
- **AUC > MIC**

PD: Response Parameters



Cmax = 9 mcg / ml

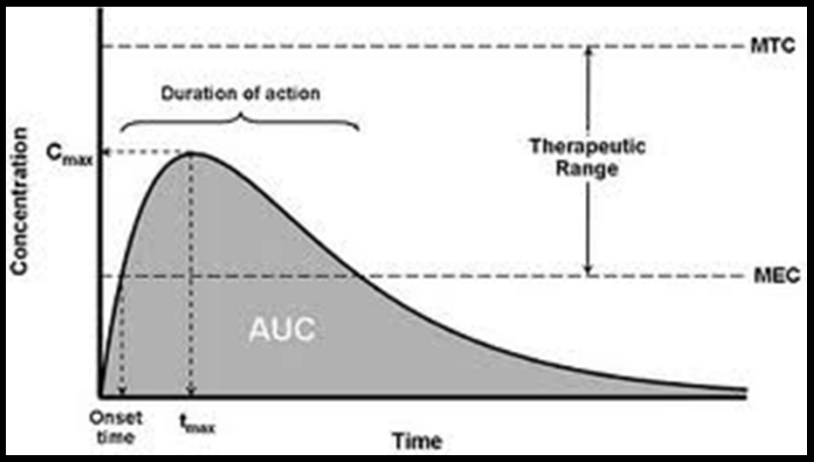
MIC = 3 mcg / ml

Cmax / MIC = 3

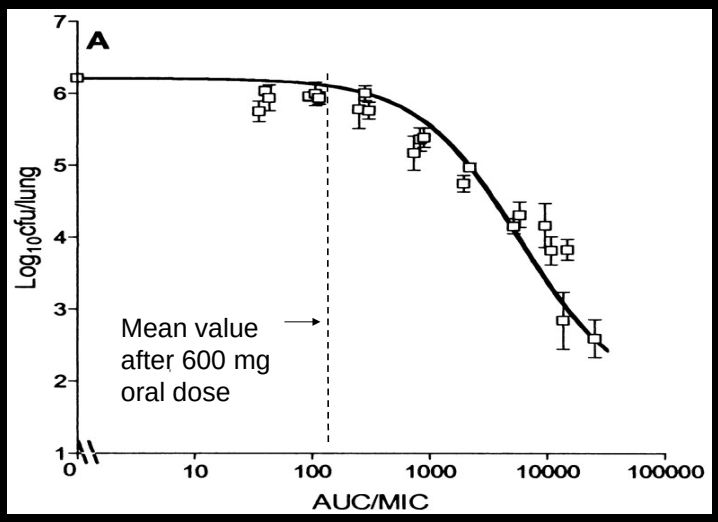
T > MIC = 8 h

AUC (mcg * h / ml)

PD: Response Parameters



PD: Sterilizing Activity of Rifampin



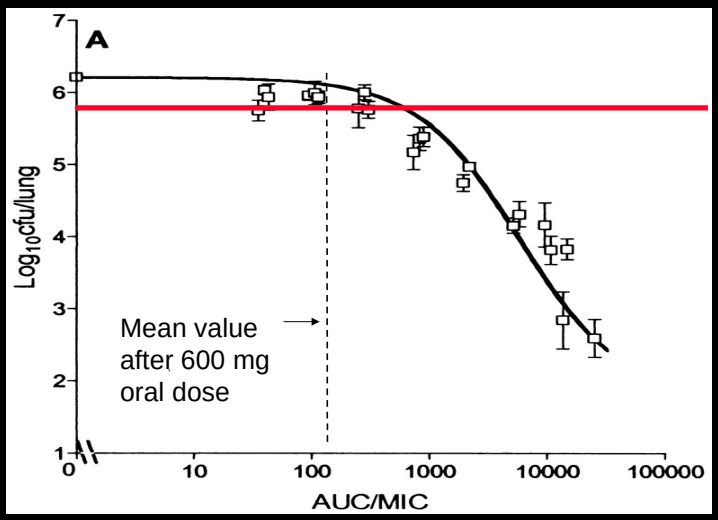
Jayaram et al, AAC (2003); 47:2118

So why is this dose - response not always apparent in the clinic ?

The main reasons that most studies to date do not define " therapeutic ranges " are:

1. Everyone got the same dose.
2. The doses are at the low end of the dose – response curve.

PD: Sterilizing Activity of Rifampin



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

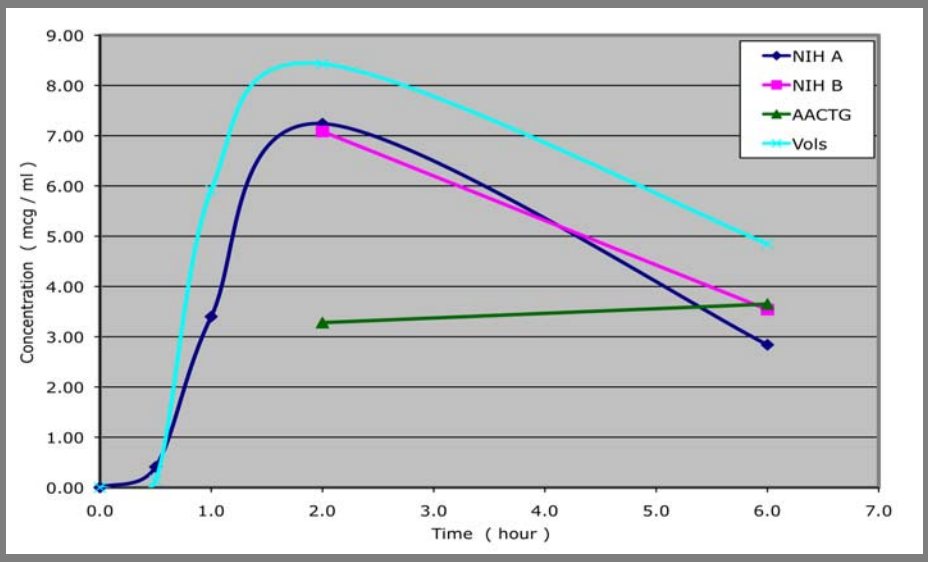
TDM with Oral TB Drugs

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

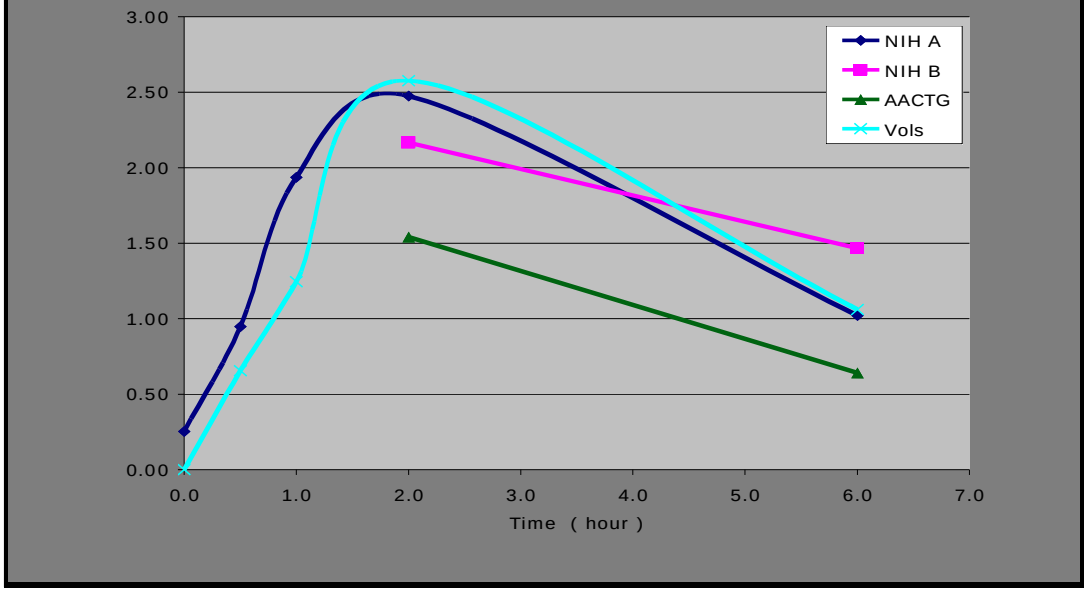
Six hour post dose blood draws generally separate delayed absorption from malabsorption.

Peloquin CA. Therapeutic Drug Monitoring in the Treatment of Tuberculosis. Drugs 2002; 62: 2169 - 2183.

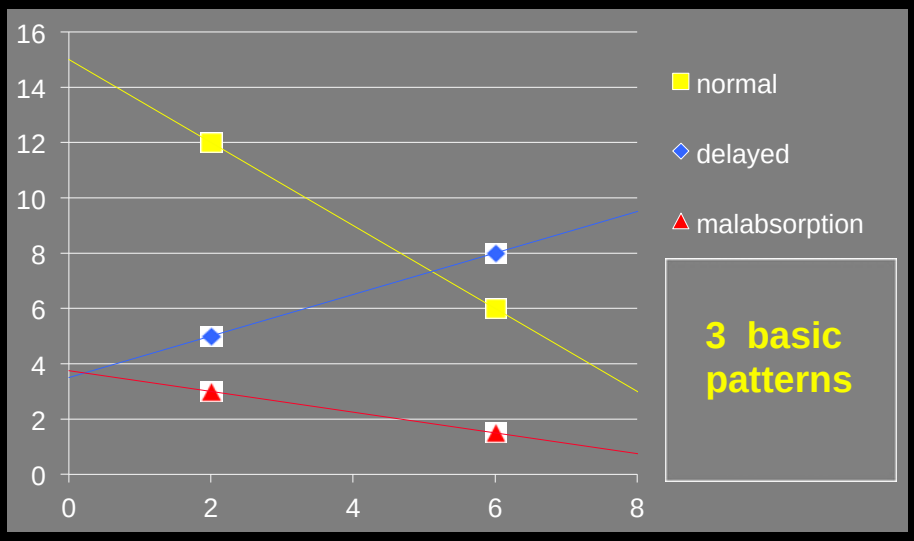
Rifampin Plasma Concentrations



Ethambutol Plasma Concentrations



Rifampin : Normal range 8 – 24 mcg / ml



So what is the big idea, anyway ?

" If you don't know where you are going,

you might wind up someplace else."

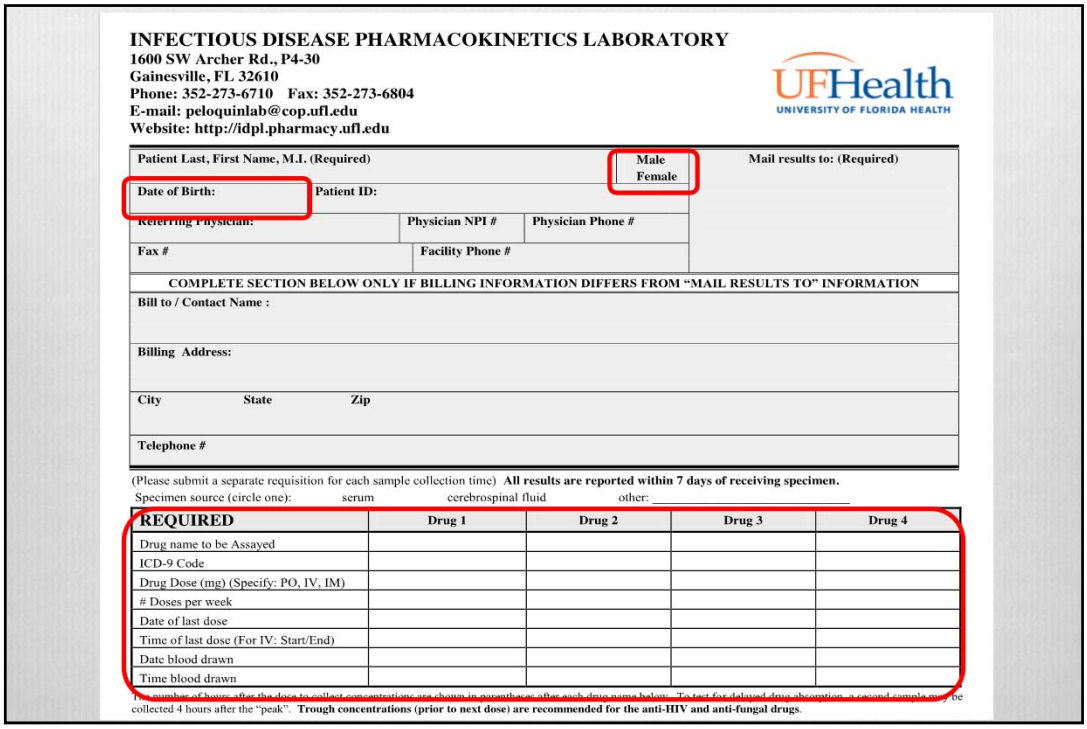
Yogi Berra

TDM – What Can Be Ordered ?

The number of hours after the dose to collect concentrations are shown in parentheses after each drug name below. To test for delayed drug absorption, a second sample may be collected 4 hours after the "peak". **Trough concentrations (prior to next dose) are recommended for the anti-HIV and anti-fungal drugs.**

Drug(s) to be assayed *(provide 2 ml serum per test)*

AMPL	Amprenavir (**trough** & 2-3 H)	EMBH	Ethambutol (2-3 H & 6-7 H)	OFLHL	Ofloxacin (2 H & 6 H)	VORL	Voriconazole (**trough**& 2 H)
ATAZ	Atazanavir (**trough** & 2 H)	ETAH	Ethionamide (2 H & 6 H)	PASH	*p*-Aminosalicylic acid (6 H)		
AZL	Azithromycin (2-3 H & 6-7 H)	ETRA	Etravirine (**trough** & 3-4 H)	POSA	Posaconazole(**trough**& 3H)		
CMH	Capreomycin (2 H & 6 H)	INH	Isoniazid (1-2 H & 6 H)	PZAH	Pyrazinamide (2 H & 6 H)		
CIPH	Ciprofloxacin (2 H & 6 H)	ITRL	Itraconazole (**trough** & 3-4 H)	RALT	Raltegravir (**trough** & 3 H)		
CLART	Clarithromycin(2-3 H &6-7 H)	LFLHL	Levofloxacin (2 H & 6 H)	RBN	Rifabutin (3 H & 7 H)		
CFH	Clofazimine (2-3 H & 6-7 H)	LNZL	Linezolid (**trough** & 2 H)	RIFH	Rifampin (2 H & 6 H)		
CSH	Cycloserine (2-3 H & 6-7 H)	LOPV	Lopinavir (**trough** & 4-6H)	RFPTN	Rifapentine (5 H & trough)		
DARU	Darunavir (**trough** & 2-4 H)	MVC	Maraviroc (**trough**& 1-2H)	SMH	Streptomycin (2 H & 6 H)		
EFVL	Efavirenz (**trough** & 5 H)	MXFL	Moxifloxacin (2 H & 6 H)	TIPV	Tipranavir (**trough** & 3 H)		



INFECTIOUS DISEASE PHARMACOKINETICS LABORATORY
1600 SW Archer Rd., P4-30
Gainesville, FL 32610
Phone: 352-273-6710 Fax: 352-273-6804
E-mail: peloquinlab@cop.ufl.edu
Website: http://idpl.pharmacy.ufl.edu

UFHealth
UNIVERSITY OF FLORIDA HEALTH

Patient Last, First Name, M.I. (Required)	Male / Female	Mail results to: (Required)
Date of Birth:	Patient ID:	
Referring Physician:	Physician NPI #	Physician Phone #
Fax #	Facility Phone #	

COMPLETE SECTION BELOW ONLY IF BILLING INFORMATION DIFFERS FROM "MAIL RESULTS TO" INFORMATION

Bill to / Contact Name :

Billing Address:

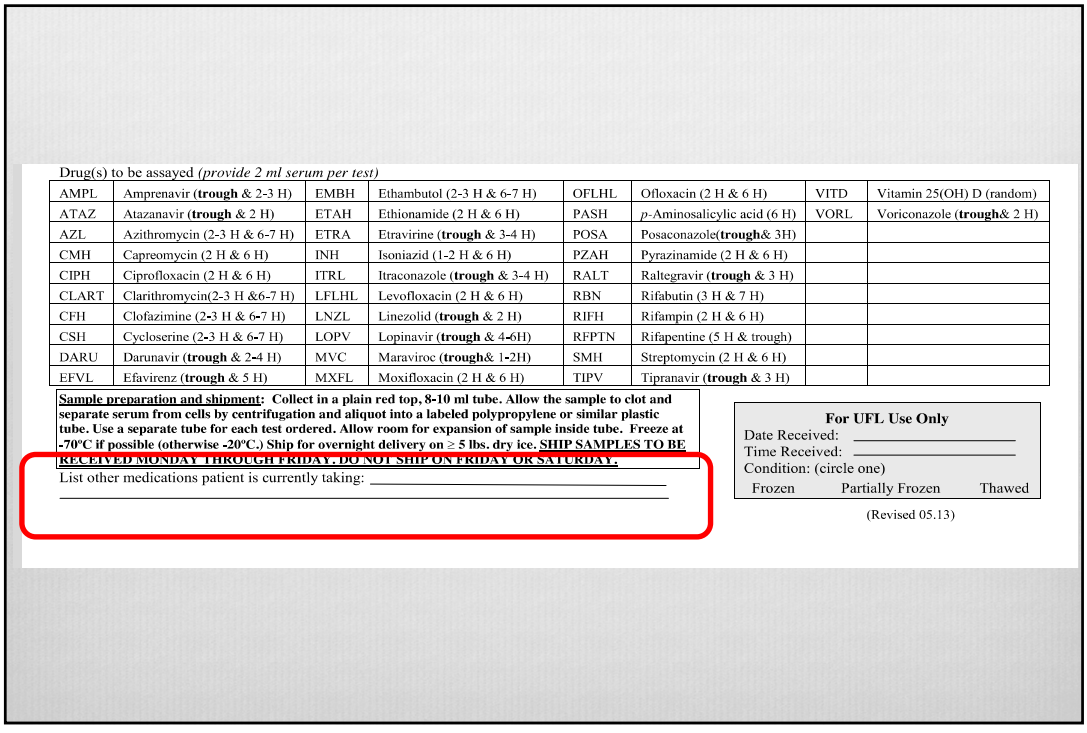
City **State** **Zip**

Telephone #

(Please submit a separate requisition for each sample collection time) **All results are reported within 7 days of receiving specimen.**
Specimen source (circle one): serum cerebrospinal fluid other: _____

REQUIRED	Drug 1	Drug 2	Drug 3	Drug 4
Drug name to be Assayed				
ICD-9 Code				
Drug Dose (mg) (Specify: PO, IV, IM)				
# Doses per week				
Date of last dose				
Time of last dose (For IV: Start/End)				
Date blood drawn				
Time blood drawn				

collected 4 hours after the "peak". **Trough concentrations (prior to next dose) are recommended for the anti-HIV and anti-fungal drugs.**



Drug(s) to be assayed *(provide 2 ml serum per test)*

AMPL	Amprenavir (**trough** & 2-3 H)	EMBH	Ethambutol (2-3 H & 6-7 H)	OFLHL	Ofloxacin (2 H & 6 H)	VITD	Vitamin 25(OH) D (random)
ATAZ	Atazanavir (**trough** & 2 H)	ETAH	Ethionamide (2 H & 6 H)	PASH	*p*-Aminosalicylic acid (6 H)	VORL	Voriconazole (**trough**& 2 H)
AZL	Azithromycin (2-3 H & 6-7 H)	ETRA	Etravirine (**trough** & 3-4 H)	POSA	Posaconazole(**trough**& 3H)		
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EFVL	Efavirenz (**trough** & 5 H)	MXFL	Moxifloxacin (2 H & 6 H)	TIPV	Tipranavir (**trough** & 3 H)		

Sample preparation and shipment: Collect in a plain red top, 8-10 ml tube. Allow the sample to clot and separate serum from cells by centrifugation and aliquot into a labeled polypropylene or similar plastic tube. Use a separate tube for each test ordered. Allow room for expansion of sample inside tube. Freeze at -70ºC if possible (otherwise -20ºC.) Ship for overnight delivery on ≥ 5 lbs. dry ice. SHIP SAMPLES TO BE RECEIVED MONDAY THROUGH FRIDAY. DO NOT SHIP ON FRIDAY OR SATURDAY.

List other medications patient is currently taking: _____

For UFL Use Only
Date Received: _____
Time Received: _____
Condition: (circle one)
Frozen Partially Frozen Thawed

(Revised 05.13)

Why Bother ?

Providing detailed information to us allows us to provide a detailed interpretation to you.

A detailed interpretation allows you to select the optimal dose as soon as possible.

Detailed Report ?

Today's date: 01-21-14
Sample tracking number: INH01171403

Laboratory:

Patient name: Joe Dirt
Patient's Facility ID number: 123456
Date of sample: 01-16-14
Time of sample: 1000 and 1400
Date of last dose: 01-16-14
Time of last dose: 0800
Amount of last dose: 900
Frequency: 3 times weekly

ISONIAZID (INH) Concentration (in mcg / mL): 2.01 mcg/ml

Today's date: 01-21-14
Sample tracking number: INH01171404

ISONIAZID (INH) Concentration (in mcg / mL): 5.41 mcg/ml

Detailed Report

ISONIAZID (INH) Concentration (in mcg / mL):

If the time of the dose and blood draw were not accurately recorded, accurate interpretation of the concentration is not possible.

The normal range for ISONIAZID (INH) serum or plasma concentrations is 3-5 mcg/ml approximately 2 hours after an oral dose. Some patients absorb INH as early as 1 hour after a dose, and the range above generally accommodates those patients at 2 hours. One hour samples may be somewhat higher. INH concentrations appear to be proportional to dose. Higher, twice or three-times weekly doses (900 mg for adults) generally produce proportionally higher INH concentrations (9-15 mcg/ml). Samples later than 2 hours after the dose often display concentrations below the normal range. Two hour plus six hour post dose samples help to distinguish between malabsorption versus delayed absorption.

INH appears to have concentration-related activity, and low INH plasma concentrations may be associated with treatment failures or relapses, especially with intermittent dosing. INH may have concentration-related peripheral neuropathy in a small number of patients. Most other potential adverse effects (hepatotoxicity, etc) do not have a clear association with plasma concentrations. Hepatic dysfunction may produce elevated INH concentrations. In most patients, renal dysfunction does not affect INH concentrations. INH concentrations above the 7 mcg/ml (daily) or 18 mcg/ml (intermittent dosing) may warrant a dose reduction, especially if the patient is vitamin B6 (pyridoxine) deficient.

Additional comments: Patient displays delayed and incomplete INH absorption. Consider 1500 mg dose and consider rechecking. C.Peloquin

If additional information is needed regarding this patient, please call Dr. Charles Peloquin at 352-273-6266.

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If additional information is needed regarding this patient, please call Dr. Charles Peloquin at 352-273-6266.

Tubes ? What tubes ?

PZA purple top 11.7% decrease

CM gold top 9% decrease

RPNT purple top 17.5% decrease

CLARI gold top 19.7% decrease

VORI gold top 38.2% decrease

POSA gold top 45.6% decrease

Tubes ? What tubes ?

Do not use purple tops.

Do not use gold tops, zebra tops, SSTs, serum separator tubes, gel tubes, or any other term for this.

Use PLAIN RED top tubes.

Usually can use green top tubes.

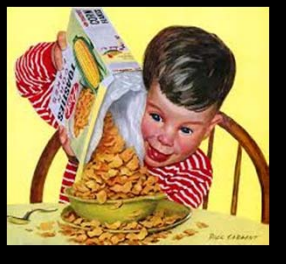
Fasted or Fed ?

First – line drugs are best taken on an empty stomach.

Avoid high fat meals.

If needed, give with a light snack, such as a cookie, graham cracker, or similar.

Once routine, then do the PK, since this will represent " the usual."



Fasted or Fed ?

Some second – line drugs are may be taken with food :

Ethionamide

PAS

Clofazimine

But not cycloserine

PK: Data Handling

The most common parameters clinically are are Cmax (peak), Cmin (trough), Tmax, & t1/2

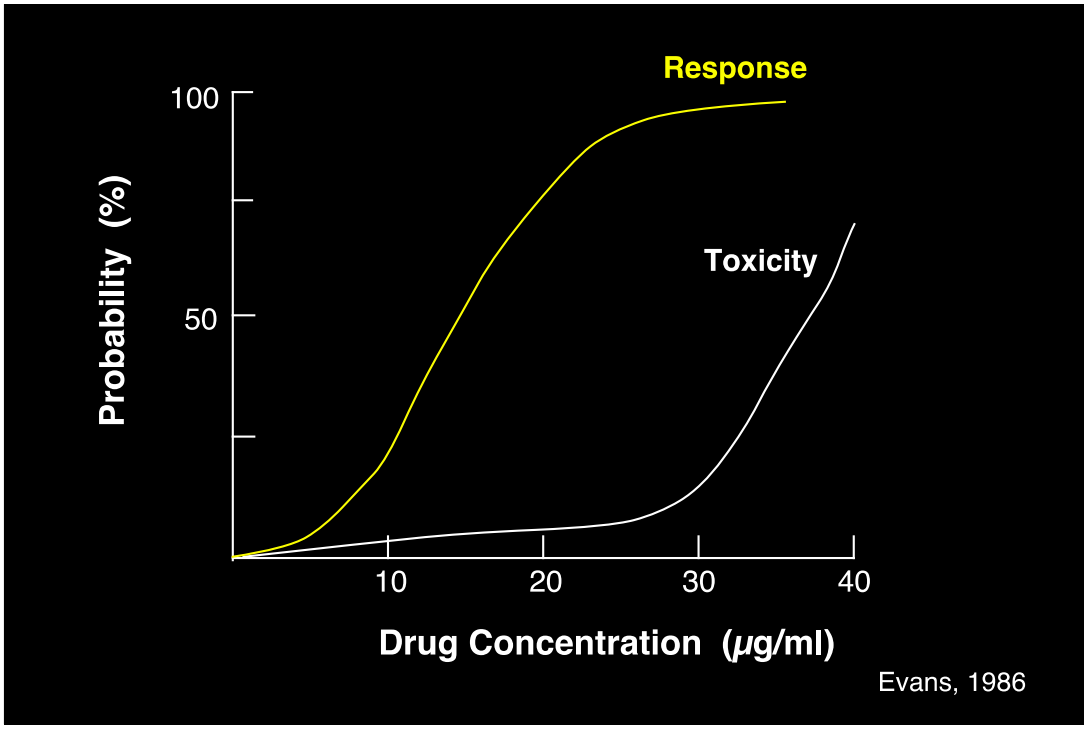
Simple kinetics can be done with a calculator, or with a spreadsheet.

The most common calculations involve linear regression (fitting a straight line to data).

Example: Amikacin Kinetics

Two Sample Conc	Infusion Hrs post dose	Ln Conc
26.30	2.00	3.27
9.40	6.00	2.24

Slope	Intercept	ke	t 1/2	Cmax	Cmax intercept
-0.26	3.78	0.257	2.69	43.99	43.99



Dosing Drugs

It is not possible to give drugs for the explicit purpose of avoiding toxicity.

To guarantee no toxicity, do not give the drug.

Dosing Drugs

If you give the drug, you must accept some probability of toxicity.

The best way to avoid toxicity is to give the most effective doses for the shortest possible time.

TDM

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.

TDM

Cost of TDM : $70 per test with

2 time points x 4 drugs = 8 tests

$560

plus, hassle, shipping costs, unfamiliarity…

Therapeutic Drug Monitoring (TDM)

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…]

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

- More info about TB, Florida, and the region is available at the Southeastern National TB Center, right here at UF !
  http://sntc.medicine.ufl.edu

- The IDP Lab Crew:
  Vaneska Mayor, Behrang Mahjoub,
  TJ Zagurski, Kyung Mee Kim, and Roger Sedlacek

  http://idpl.pharmacy.ufl.edu

Questions ?

“ I wish I had an answer to that,

because I'm tired of answering that question.

Yogi Berra