Therapeutic Drug Monitoring in People on ART and Anti – Tubercular Drugs

Charles A. Peloquin, Pharm. D.
Professor and Division Head, Translational Research
Director, Infectious Disease Pharmacokinetics Lab.
Jack C. Massey Endowed Professor
University of Florida

October, 2022

Disclosures

Dr. Peloquin has no relevant financial disclosures.

Dr. Peloquin directs a not – for – profit clinical laboratory that performs TDM.

Dr. Peloquin does not work on commission.

“ How come you get to talk about this ? ”

1. 2 - year fellowship in infectious diseases and pharmacokinetics (PK) in Buffalo, NY
2. 20 years as director of PK at National Jewish Health in Denver, CO
3. 13 years as director of PK at UF COP in Gainesville, FL
4. Over 220 peer – reviewed original research papers on the topic of PK and PD

Aims

1. Review underlying principles of antibiotic action, pharmacokinetics, and pharmacodynamics

2. Describe specific examples of Therapeutic Drug Monitoring (TDM) in specific types of patients.

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.

Dosing Drugs

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

Guessing (also known as one size fits all)

and

Knowing (also known as personalized medicine)

Dosing Drugs

Example One

Guessing I will give all patients 5 mg warfarin and
I will not check INRs

or

Knowing I will give all patients adjusted warfarin and
I will check INRs on all patients

Dosing Drugs

Example Two

Guessing I will give all patients 10 U insulin TID and
I will not check glucose.

or

Knowing I will give all patients adjusted insulin and
I will check glucose on all patients.

Dosing Drugs

Examples

Guessing Is that the standard of practice ?
No, it would be considered malpractice.

or

Knowing This is the standard of practice.
Almost every type of drug therapy uses some form of direct feedback.

Dosing Drugs

Example Three

Guessing I will give all patients the same dose of antimicrobials and I will not check concentrations.

or

Knowing I will start renal - adjusted doses of antimicrobials and I will check concentrations.

Dosing Drugs

Example Three

Guessing The old standard of practice.

or

Knowing The emerging standard of practice.

Dosing Drugs

You may have seen …

J Antimicrob Chemother
doi:10.1093/jac/dkab011

Journal of Antimicrobial Chemotherapy

The case for 'conservative pharmacotherapy'

Sarah C. J. Jorgensen[1]*, Jackson J. Stewart[2] and Bruce R. Dalton[3]

[1]Department of Pharmacy, Mount Sinai Hospital, Toronto, ON, Canada; [2]Pharmacy Services, University of Alberta Hospital, Edmonton, AB, Canada; [3]Pharmacy Services, Alberta Health Services, Calgary, AB, Canada

Dosing Drugs

A rebuttal from :

" The Case for Precision Dosing,
Medical Conservatism Does Not Justify Inaction "

Marc H. Scheetz, Thomas P. Lodise, Kevin Downes,

George Drusano, Michael Neely

Dosing Drugs

A few salient points :

Adequate evidence exists to conduct TDM and precisely target antibiotic exposures.

Achievement of any antibiotic concentration does not guarantee efficacy or avoidance of toxicity.

Stochastic control optimizes the probability of achieving favorable responses across patients.

Dosing Drugs

A few salient points :

Variability in targets (such as the organism's MIC) can be considered with models.

That is, complexity alone does not relegate the decision - making framework to "clinician intuition".

There has never been a prospective randomized clinical trial of "clinician intuition".

Dosing Drugs

A few salient points :

“ We call for randomized, controlled trials of TDM. However, we suggest that these trials are not necessary to make TDM the standard of care for multiple classes of antibiotics.”

Dosing Drugs

You can do better than guessing and intuition.

"That's all I have to say about that."

Forrest Gump

Dosing Drugs

What is the key difference?

Addressing inter – individual variability.

It would be very convenient if humans were clonal, or at least inbred.

Unfortunately for those dosing drugs,
most humans are outbred.

Pharmacokinetics (PK)

The study of the movement of drugs through the body.

Most commonly based on the study of plasma concentrations (plural) in relation to dose.

Pharmacokinetics (PK)

Are we there yet ?

Distance = Rate x Time

You need 2 variables to solve the equation.

Otherwise, you can only guess.

In PK, you need 2 time points to determine a trajectory. Otherwise, you can only guess.

Pharmacokinetics (PK)

With a *single sample*, it is not possible to study the movement of drugs.

***Single samples* provide a snap - shot in time.**

That is called *pharmaco - statics*.

Stop doing that.

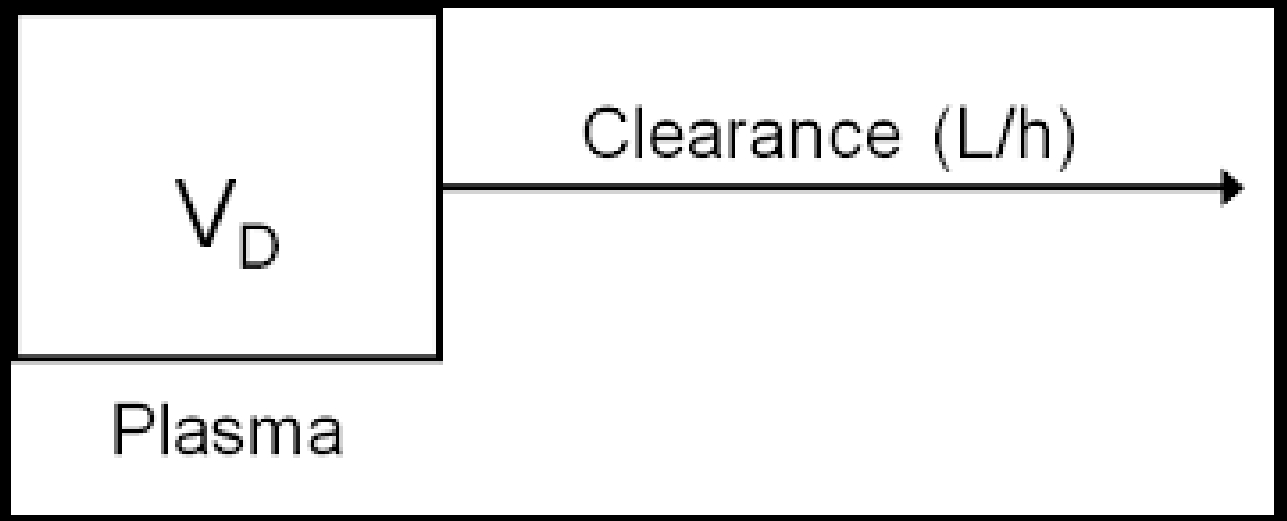
Applied Pharmacokinetics (PK)

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

Also known as therapeutic drug monitoring, or TDM.

Applied Pharmacokinetics (PK)

We are going to talk about a box and an arrow.



Applied Pharmacokinetics (PK)

The simplest PK model is a one compartment model.

For an I.V. drug, this includes two parameters : volume of distribution V and clearance Cl.

To adequately describe the simplest model, you need at least 1 plasma sample PER parameter.

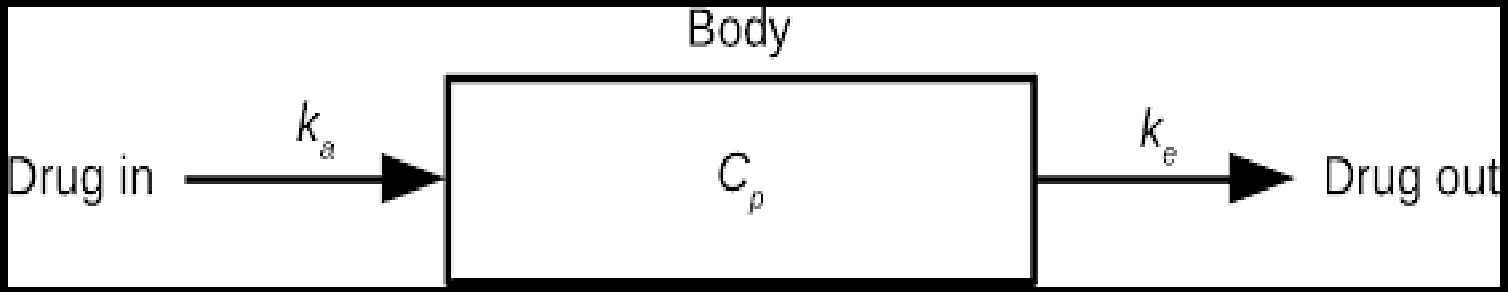
Applied Pharmacokinetics (PK)

V usually is best captured near the time of **peak concentration.**

Cl usually is best captured near the time of **trough concentration** (but *not* with a zero).

Oral doses add an absorption rate constant **ka.** Because oral absorption can be **delayed** by food or disease, **2 samples** usually are required to adequately assess the rate and extent of absorption.

Applied Pharmacokinetics (PK)



Instead of Cl, one can use an elimination rate constant ke as a PK parameter.

Half - life t1/2 is calculated from ke.

PK: Plasma Elimination Half - Life

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

After 5 - 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.

PK: Clearance and Volume

t 1/2 is directly proportional to the volume of distribution V.

t 1/2 is inversely proportional to the clearance of a drug Cl.

Thus, you need info on V and Cl to estimate t1/2 and to do kinetics.

Linear Kinetics

Two Sample Infusion

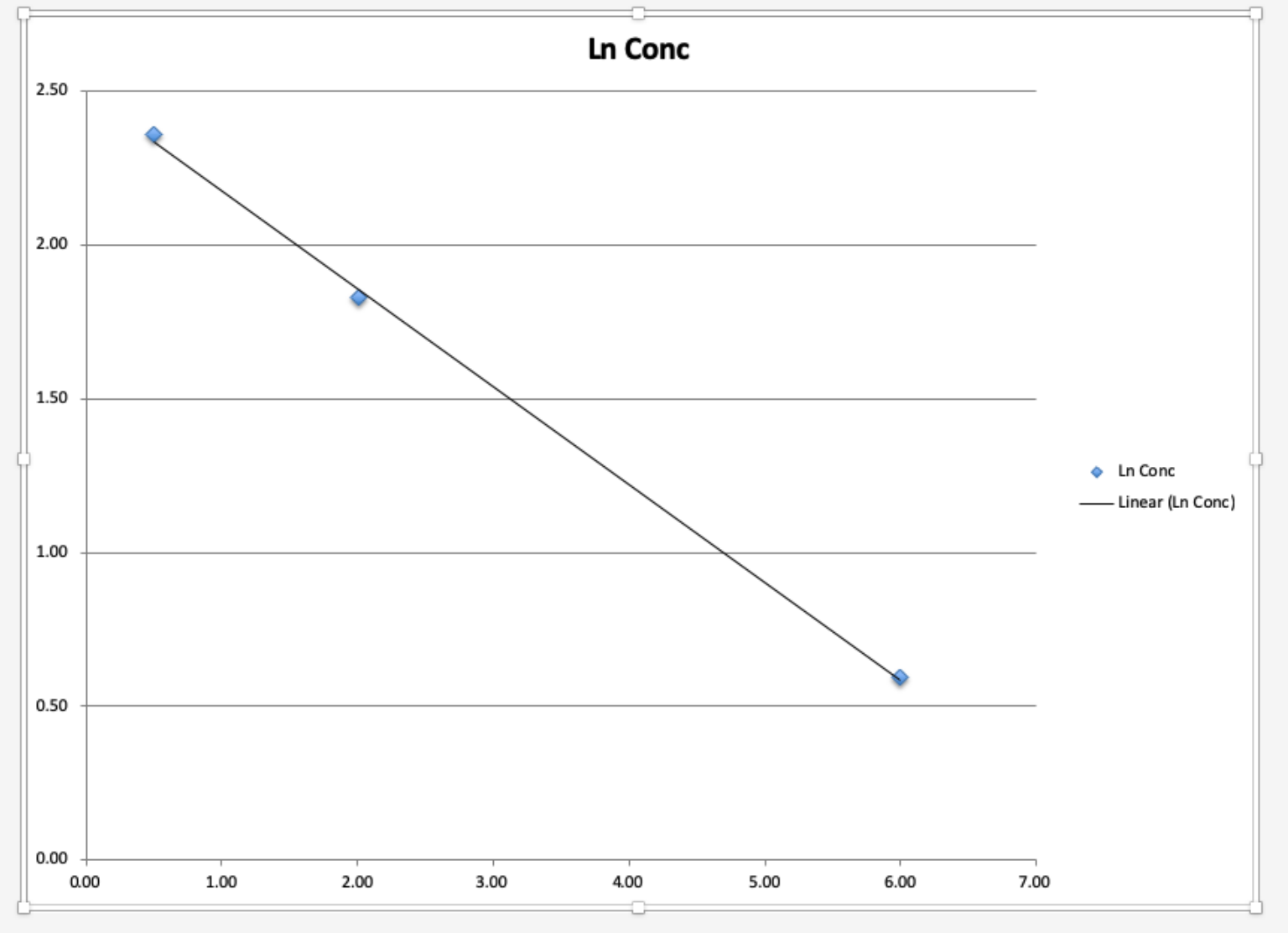
Conc	Hrs post dose	Ln Conc
26.30	2.00	3.27
9.40	6.00	2.24

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

You must have accurate times of dose and draws.

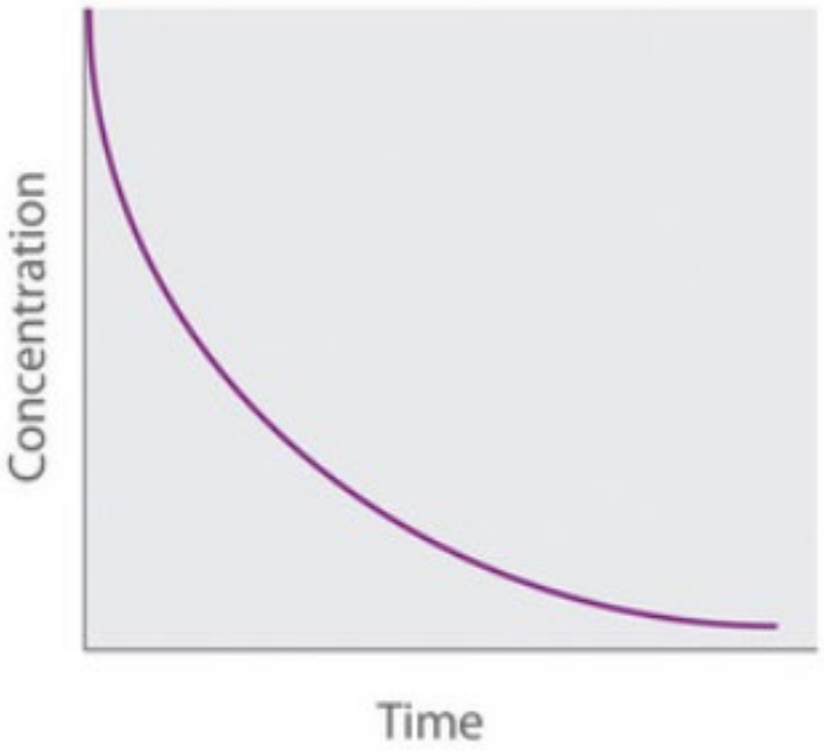
Linear Kinetics : Ln Conc vs. Time

Ln Conc



Time

Linear Kinetics : Ln Conc vs. Time



https://chem.libretexts.org/Bookshelves/Physical_and_Theoretical_Che…Kinetics/Experimental_Methods/Methods_of_Determining_Reaction_Order

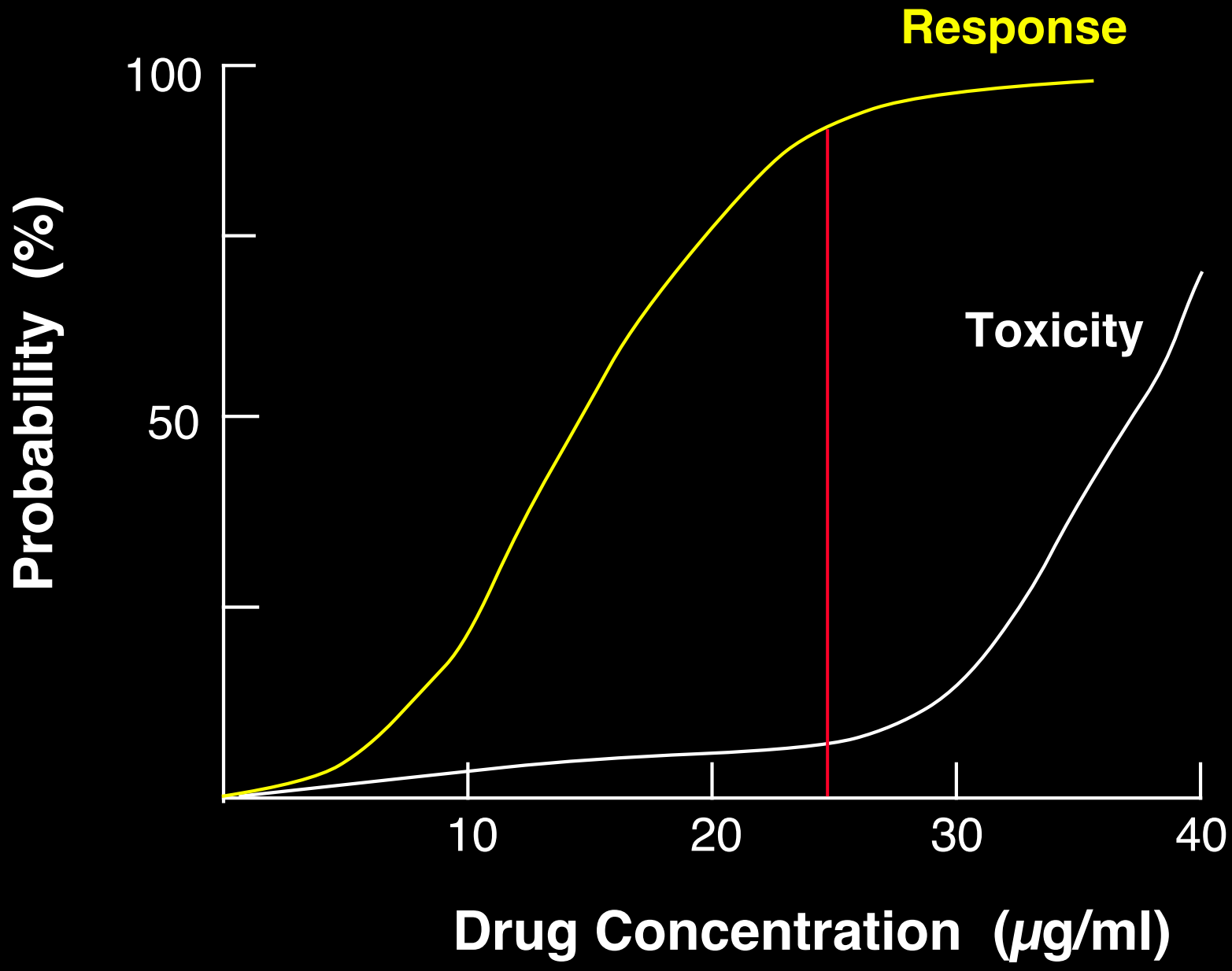
Therapeutic Drug Monitoring (TDM)

aims to promote optimum drug treatment

by maintaining serum drug concentrations

within a "normal range," or preferably

a "therapeutic range"


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

Evans, 1986

Therapeutic Drug Monitoring (TDM)

It is very important to understand that not all toxicity is concentration – related.

Events such as GI intolerance or rashes occur simply because you gave the drug and the patient did not tolerate it.

What TDM is not

TDM is not a "no pest strip" to ward off medical – legal actions.

TDM done poorly offers you no protection.

Your job is to protect the patient, and you can use TDM to do that.

Azole Anti - fungals

Numerous reports have documented improved outcomes when VORI trough concentrations are maintained above 1 mg / liter.

However, the trough concentration is really only a surrogate for AUC, which is the likely driver of voriconazole efficacy.

Without advanced software, it is very hard to accurately estimate AUC from a single trough concentration.

Neely M. et al. Antimicrob Agents Chemother 2015 59: 3090 –3097.

Azole Anti - fungals

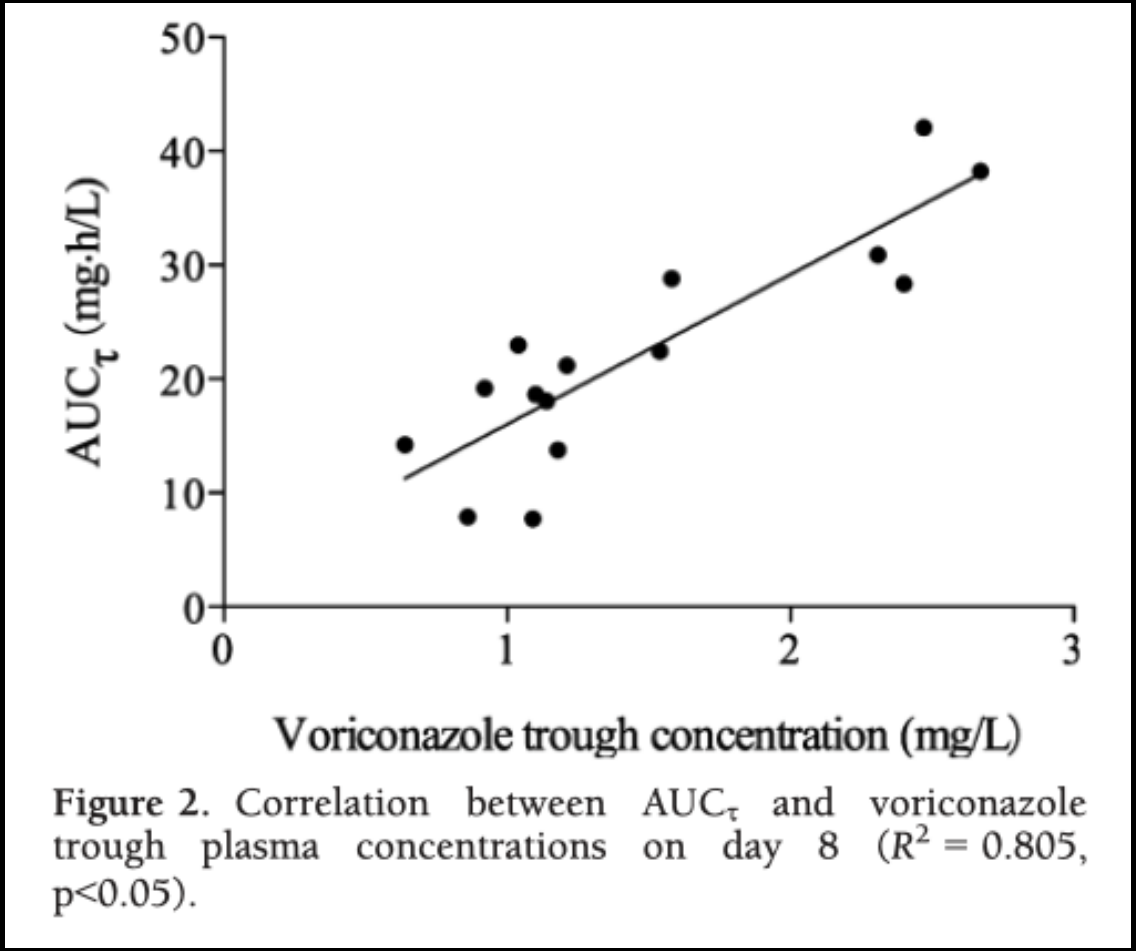


Figure 2. Correlation between AUC_τ and voriconazole trough plasma concentrations on day 8 ($R^2 = 0.805$, $p<0.05$).

AUC = Dose / CL

AUC, and therefore dose, can vary 5 fold !

Wang T et al. Pharmacotherapy 2015; 35 (9) : 797–804

Azole Anti - fungals

Solitary trough concentrations are not sufficiently informative.

Azoles are AUC / MIC driven drugs.

Troughs alone tell you nothing about the extent of absorption or volume (Vd).

They do not directly indicate what dose adjustment would be appropriate.


Voriconazole troughs
9
8
7
6
5
4
3
2
1
0
0
2
4
6
8
10
12
14
High
Moderate
Low

Anti – HIV INSTIs

Dolutegravir and bictegravir are key drugs in the treatment of HIV.

They both may be subject to drug interactions, especially with rifamycins.

Measuring concentrations early in treatment can confirm the adequacy of the dose.

Typically, a trough and a 2-hour post dose sample is adequate.

Hepatitis C Drugs

Ledipasvir and **sofosbuvir** are key drugs in the treatment of HCV.

They both may be subject to **drug interactions,** especially with **rifamycins.**

Measuring concentrations early in treatment can confirm the adequacy of the dose.

Typically, a trough and at 1 and 4 hours post dose sample is adequate.

Hepatitis C Drugs

Manuscript in progress :

Successful Treatment and Cure of both TB / HCV in Coinfected Patients with the Utilization of Therapeutic Drug Monitoring

Hepatitis C Drugs

Manuscript in progress :

Five cases of successful intentional, concomitant treatment to cure of both TB and HCV with first line agents, using TDM.

Appropriate dosage adjustments were assured for both the TB and HCV medications to attain expected serum concentrations throughout the duration of treatment.

TDM at UF

AZL	Azithromycin (2-3 H & 6-7 H)	ETAH	Ethionamide (2 H & 6 H)	PZAH	Pyrazinamide (2 H & 6 H)	β-Lactams (intravenous doses) (30-60 min. post infusion & **trough**)	
BDQ	Bedaquiline (5 H & 24 H)	INH	Isoniazid (1-2 H & 6 H)	RBN	Rifabutin (3 H & 7 H)		
BIC	Bictegravir (**trough** & 2 H)	ITRL	Itraconazole (**trough** & 3-4 H)	RIFH	Rifampin (2 H & 6 H)	PIPE	Piperacillin
CIPH	Ciprofloxacin (2 H & 6 H)	LDV	Ledipasvir (**trough**& 4 H)	RPNT	Rifapentine (**trough** & 5-6H)	AMOX	Amoxacillin
CLART	Clarithromycin (2-3H&6-7 H)	LFLHL	Levofloxacin (2 H & 6 H)	RILP	Rilpivirine (**trough** & 4-5H)	AMPI	Ampicillin
CFH	Clofazimine (2-3 H & 6-7 H)	LNZL	Linezolid (**trough**, 2 & 5-6 H)	SOF	Sofosbuvir (**trough**& 1 H)	AZTRE	Aztreonam
CSH	Cycloserine (2-3 H & 6-7 H)	LOPV	Lopinavir (**trough** & 4-6H)	VORL	Voriconazole (**trough**& 2 H)	CEFAZ	Cefazolin
DARU	Darunavir (**trough** & 2-4 H)	MXFL	Moxifloxacin (2 H & 6 H)			CEFE	Cefepime
DTG	Dolutegravir (**trough** & 2 H)	PASH	*p*-Aminosalicylic acid (6 H)			CEFT	Ceftriaxone
EFVL	Efavirenz (**trough** & 5 H)	PMD	Pretomanid (5 H & 24 H)	NAFC	Nafcillin	IMIP	Imipenem
EMBH	Ethambutol (2-3 H & 6-7 H)	POSA	Posaconazole (**trough**& 3H)	MERO	Meropenem	OXA	Oxacillin

Therapeutic Drug Monitoring (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.

Role for PK in Treating TB

TDM allows you to individualize therapy.

TDM allows you to optimize the pharmacodynamically - linked variable.

Thanks

- The University of Florida IDPL Team :

  TJ Zagurski, Kyung Mee Kim, Yufei Tang,
  Alveena Mathew, Jessie Liu, Mohammad Alshaer,
  Nicole Maranchick, Stacy Stoneberger

http://idpl.pharmacy.ufl.edu