

Between Dose and Response: Pharmacokinetics, Pharmacodynamics, and Statistics

Scope Academy 2008

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Outline

1. Introduction – Why is a *statistician* giving this lecture?
2. What is *pharmacokinetics* (PK)?
3. What is *pharmacodynamics* (PD)?
4. “*Population PK/PD*” and statistics
5. Concluding remarks

Warning: There are just a few *equations* in this lecture!

1. Introduction

What do we want in a drug?

- *Safety*
- *Efficacy* and *effectiveness*

Can people take it without bad stuff happening, and does it work?

The usual paradigm: Look at “*what goes in*” and “*what comes out*”

- For a *response* that we hope the drug affects (e.g., clotting index, headache severity, survival time, etc.) if we were to administer the drug at some dose to the *population* of patients, what would the *average response* be?
- ... And how does it *compare* to the *average response* for *competing drugs* or for *other doses* of this drug?
- ... And do any *bad side effects* (*toxicities*) occur?

1. Introduction

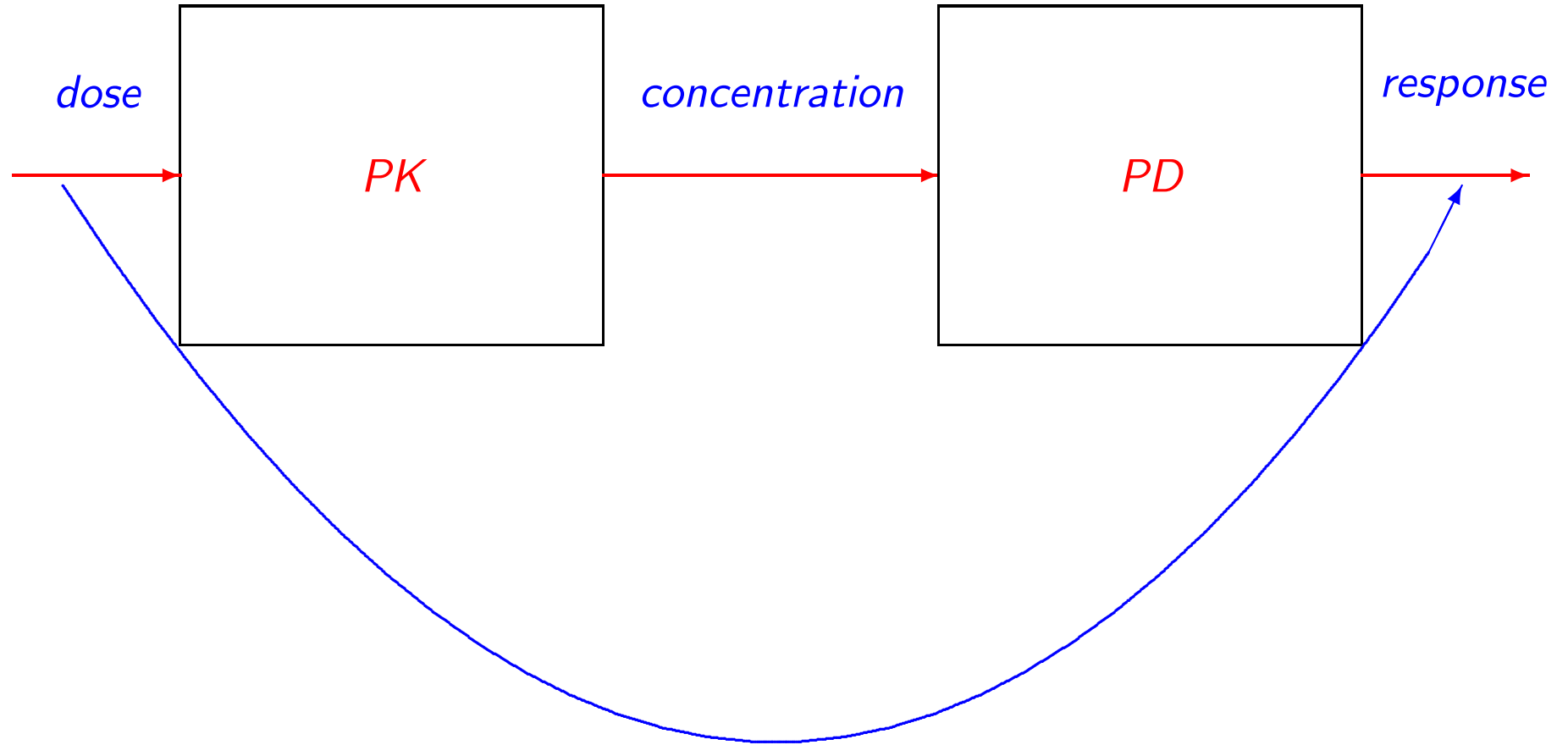
Key message: Understanding what goes on *between dose* (administration) and *response* can yield insight on

- How best to choose doses at which to evaluate a drug
- How best to use a drug in a population
- How best to use a drug to treat individual patients or subpopulations of patients
- ... And a lot more

Key concepts:

- *Pharmacokinetics* (*PK*) – “what the body does to the drug”
- *Pharmacodynamics* (*PD*) – “what the drug does to the body”

1. Introduction



1. Introduction

So why is a statistician giving this lecture? Understanding what goes on *between dose* (administration) and *response*

- Relies *critically* on combining physiological (mathematical) modeling with *statistical modeling*
- *Statistical modeling* is an integral part of the *science*
- “*Population PK*” and “*Population PK/PD*”

2. What is Pharmacokinetics?

“What the body does to the drug”

Goals of drug therapy: From a pharmacologist’s point of view, for an individual patient or type of patient

- Achieve a *therapeutic objective* (cure disease, mitigate symptoms, etc.)
 - Minimize *toxicity* (undesirable or dangerous side effects)
 - Minimize *difficulty of administration*
- ⇒ Identify *dosing regimens* to address these issues

2. What is Pharmacokinetics?

Implementation of drug therapy: To achieve this, must determine

- How *much*? How *often*?
- To *whom*? Different for *different patients*? *ages*? *genders*?
- Under what *conditions*? E.g., *with food*? *without another drug*?

Information on this: *Pharmacokinetics*

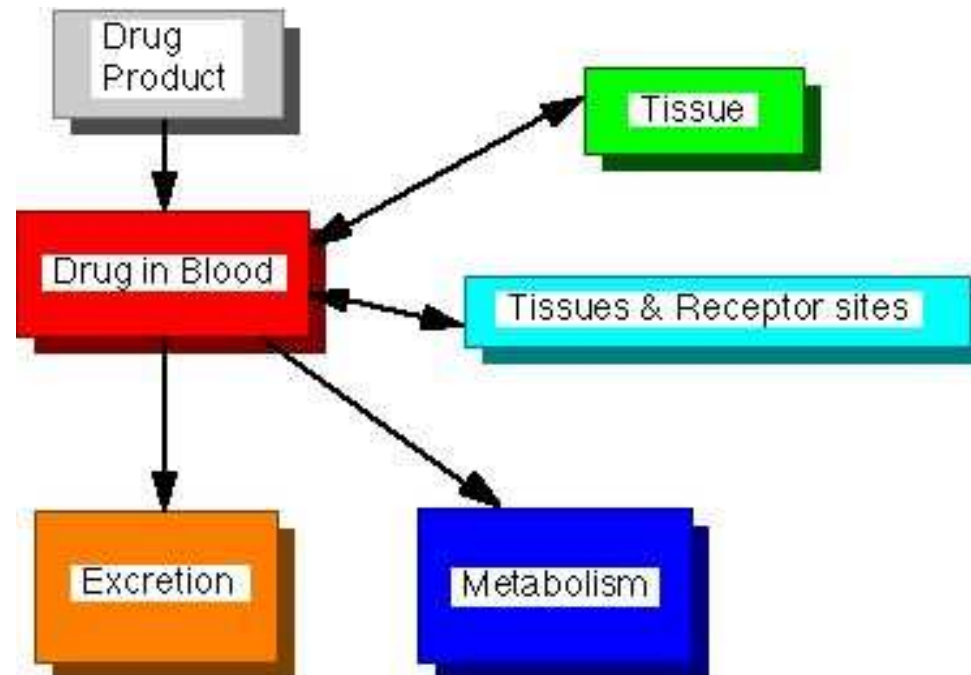
- Study of how the drug *moves* through the body and the *processes* that govern this movement



(*Elimination* = *metabolism* and *excretion*)

2. What is Pharmacokinetics?

What goes on inside: *ADME*



Routes of drug administration: *Intravenously, Orally, Intramuscularly, Subcutaneously ...*

2. What is Pharmacokinetics?

Basic assumptions and principles:

- There is a “*site of action*” where drug will have its effect
- Magnitudes of *response*, *toxicity* depend on *drug concentration* at the site of action
- Drug cannot be placed *directly* at site of action, *must* move there
- Concentrations at site of action are *determined* by *ADME*
- Concentrations must be kept *high enough* to produce a desirable response, but *low enough* to avoid toxicity

⇒ “*Therapeutic window*”

- *Cannot* measure concentration at site of action directly, but *can* measure in *blood/plasma/serum*; reflect those at site

2. What is Pharmacokinetics?

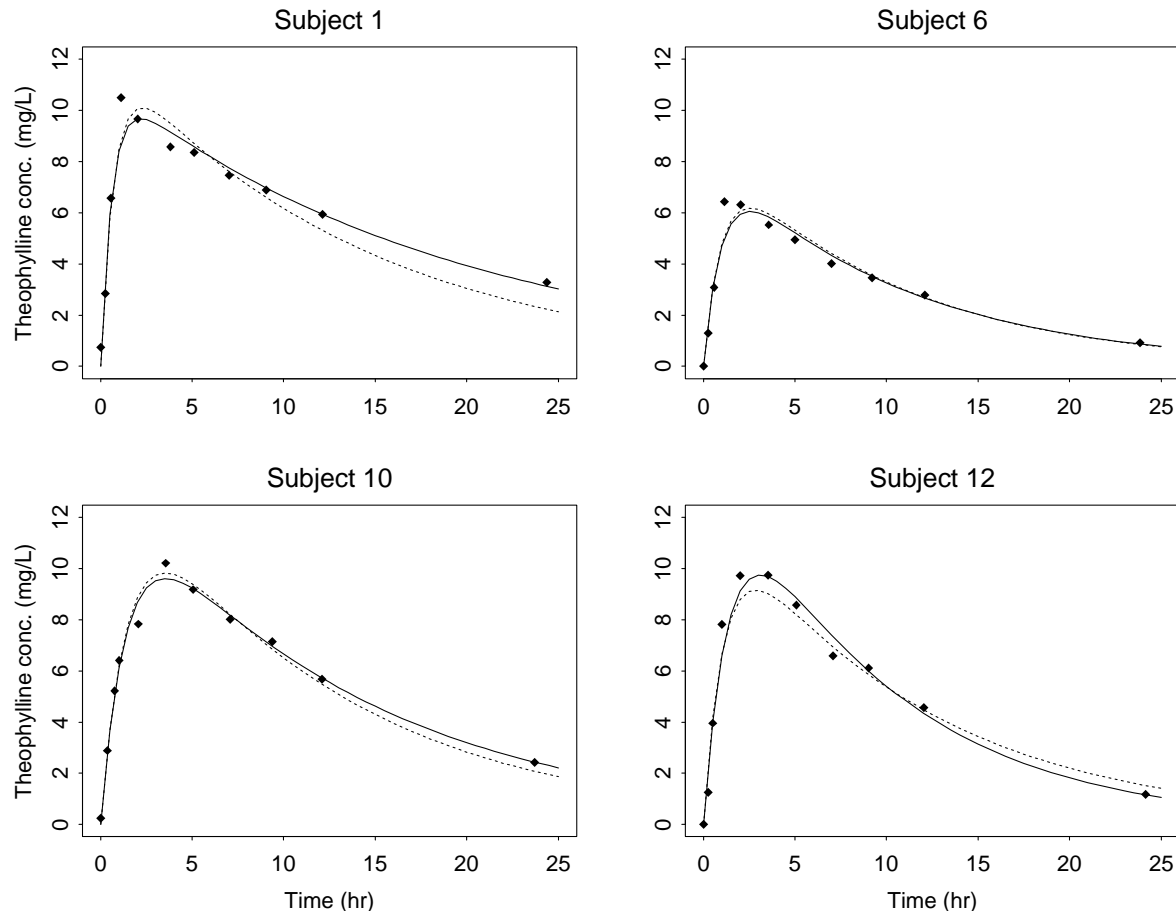
Approach:

- ADME dictates *concentrations* at site of action, but ADME can not be observed *directly*
- Understanding ADME allows manipulation of *concentrations* through different *dosing strategies* (*coming up...*)
- *Plasma concentrations* have information about ADME \implies measure *concentration over time* to learn about ADME

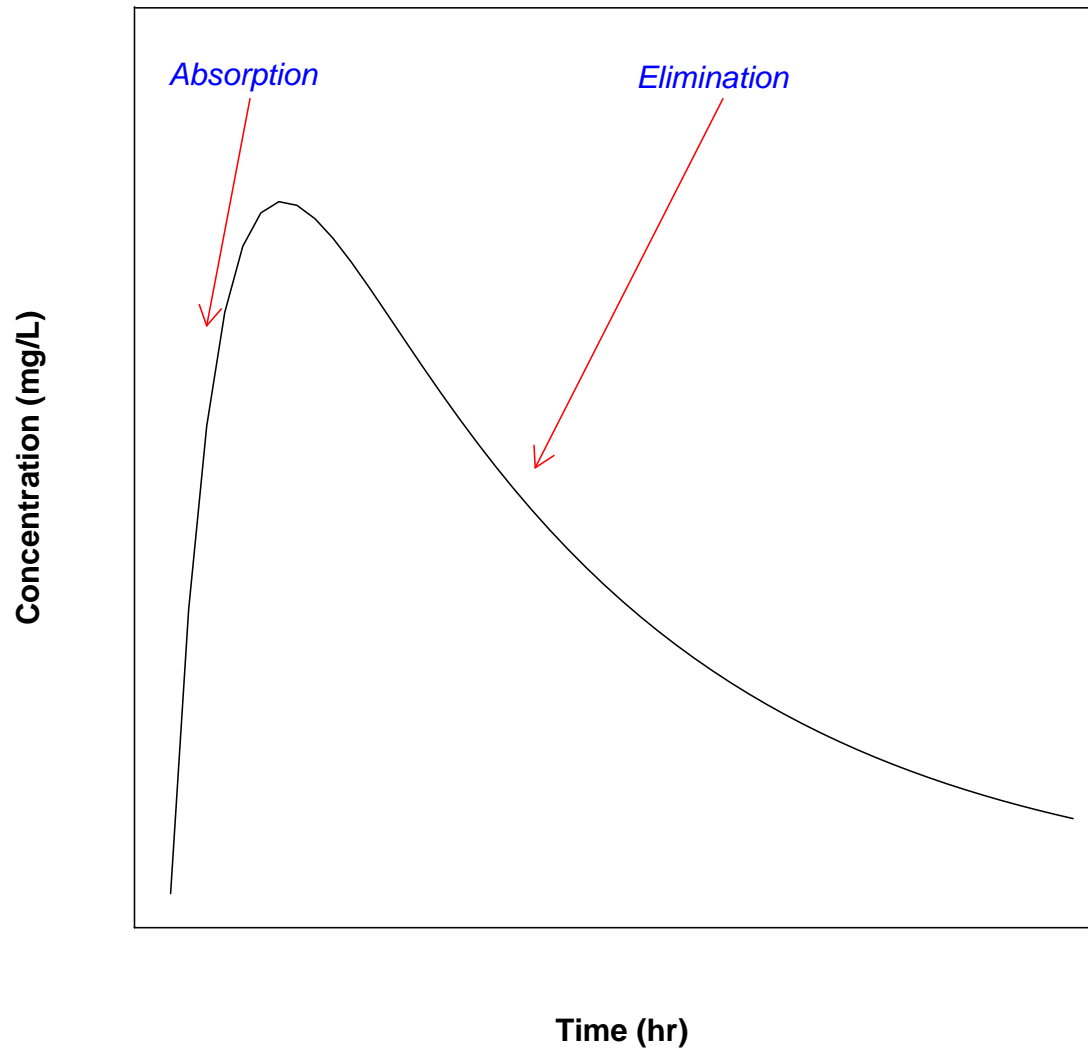
PK study: Collect concentration-time data from a *sample* of subjects from the *population* to learn about ADME

2. What is Pharmacokinetics?

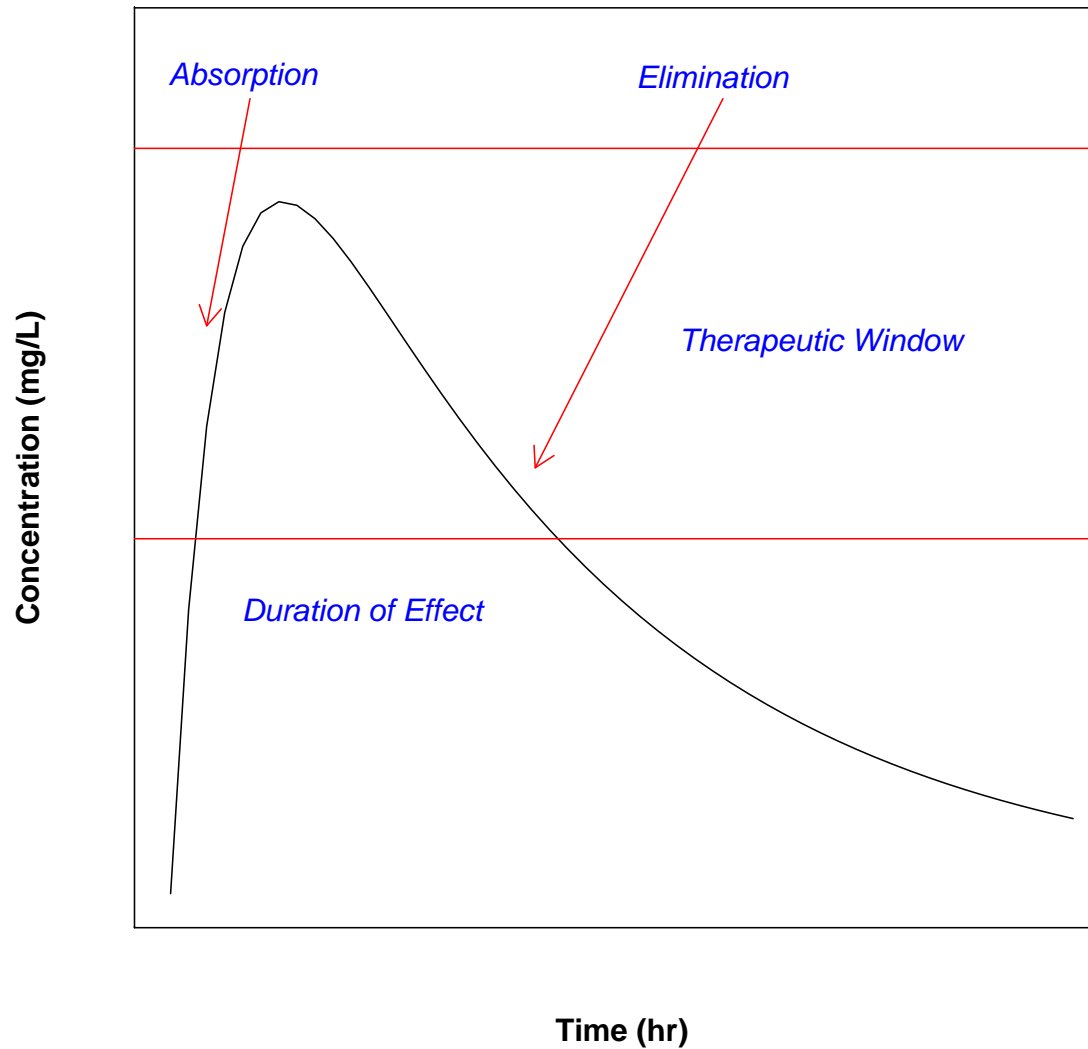
Data for 4 subjects given the same oral dose of anti-asthmatic theophylline:



2. What is Pharmacokinetics?



2. What is Pharmacokinetics?



2. What is Pharmacokinetics?

Multiple dosing: Ordinarily, *sustaining doses* are given to *replace* drug eliminated, *maintain* concentrations in therapeutic window over time

- *Steady state*: amount lost = amount gained

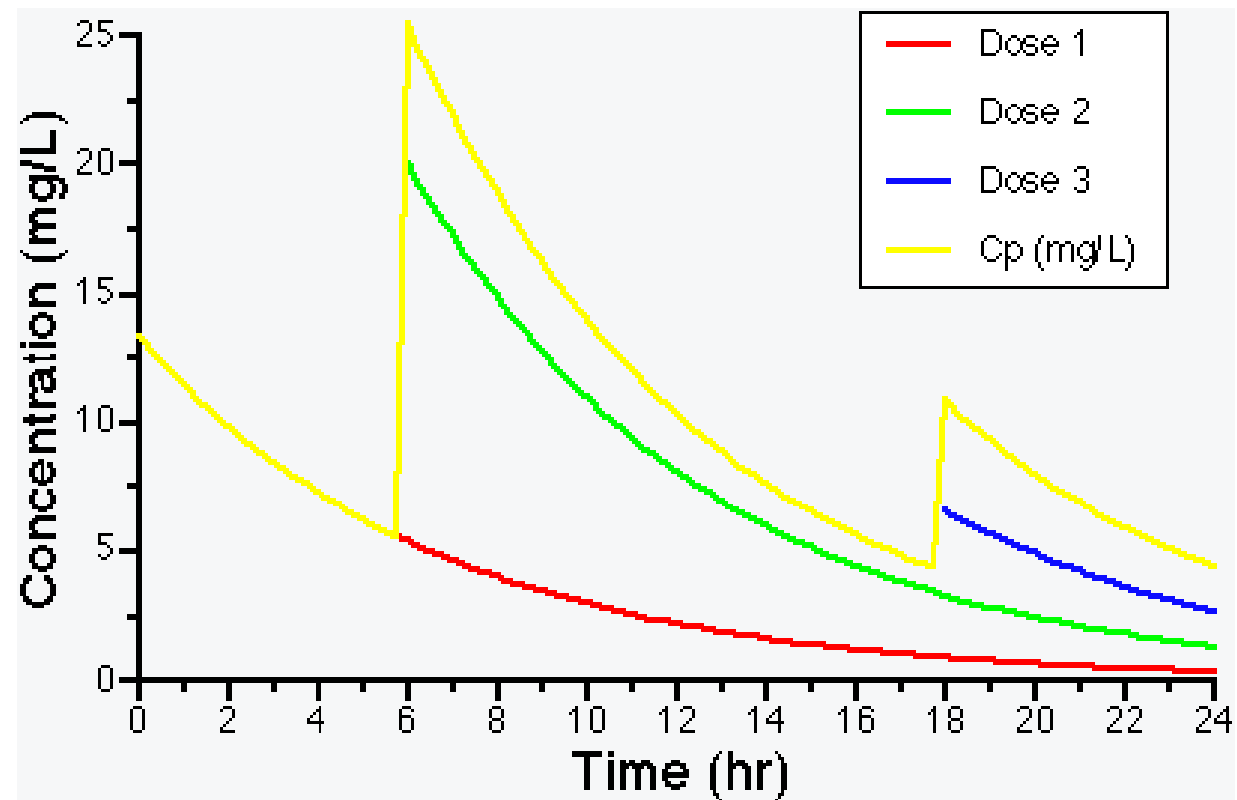
Frequency, amount for multiple-dose regimen governed by:

- *ADME*
- *Width* of therapeutic window

Ultimate objective: Determine *multiple dosing regimens* that keep concentrations in the therapeutic window...

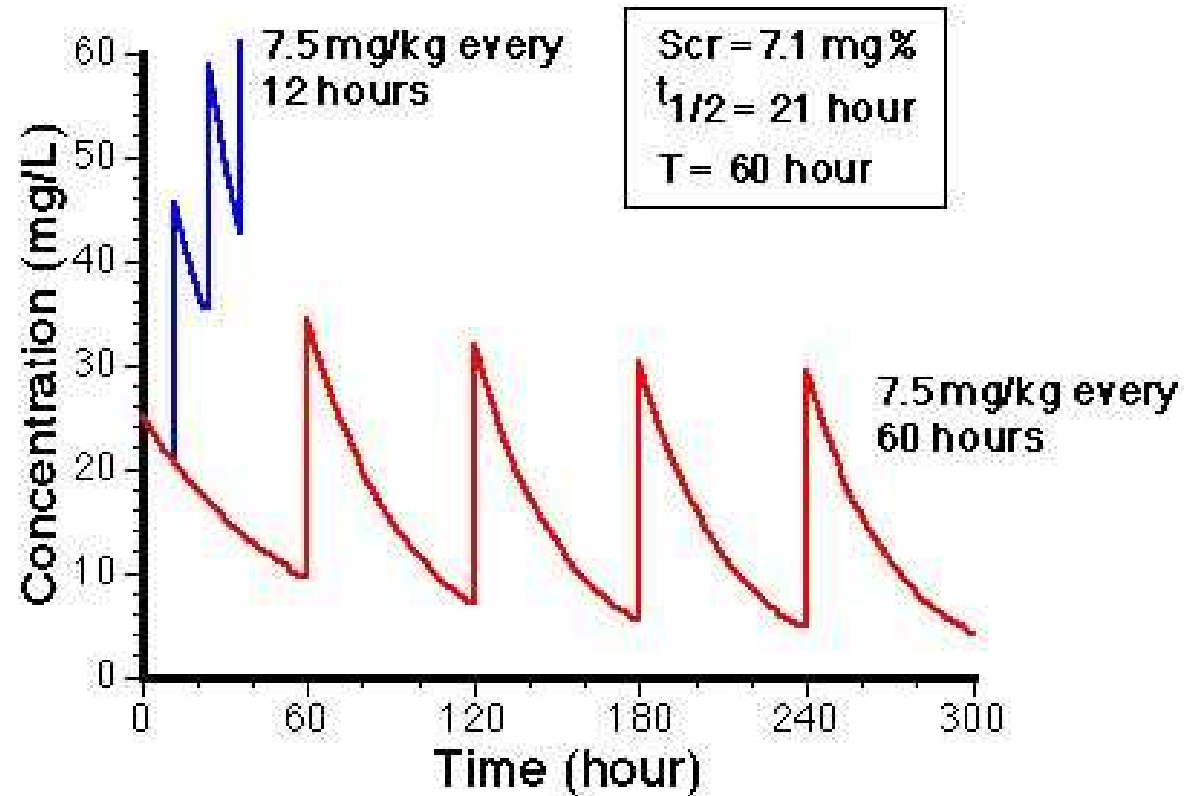
2. What is Pharmacokinetics?

Principle of superposition:



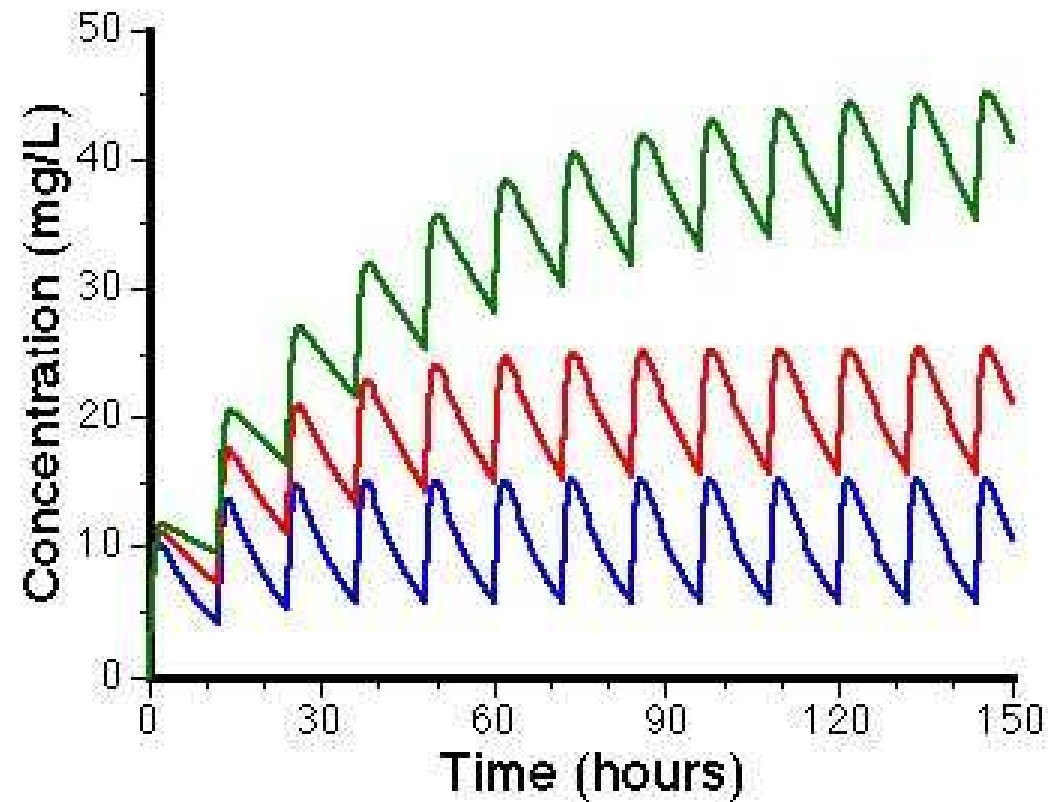
2. What is Pharmacokinetics?

Effect of different frequency: Same dose and ADME characteristics



2. What is Pharmacokinetics?

Effect of different elimination characteristics: Same dose and frequency



2. What is Pharmacokinetics?

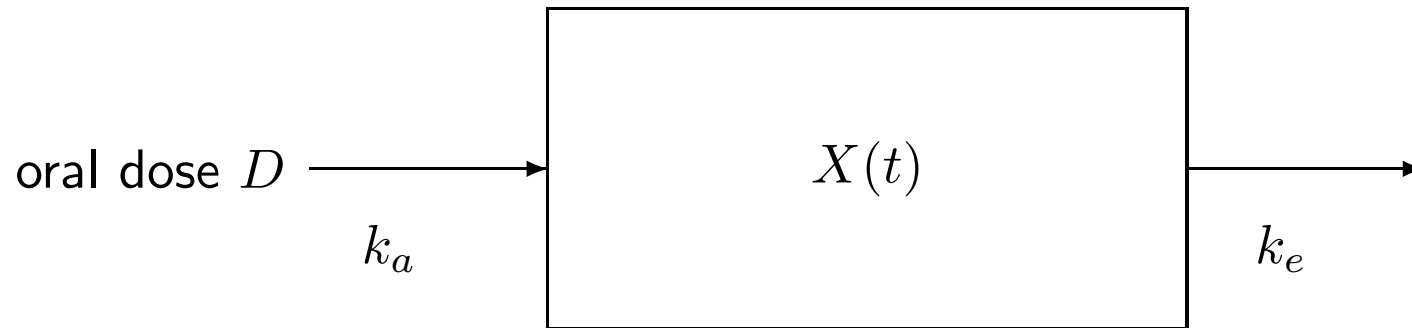
Need a way to learn about ADME from plasma concentrations...

Compartmental modeling: Represent *the body* of an individual subject by a system of *compartments* depending on *ADME* processes

- Can be *grossly simplistic*, but often gives a good enough approximation to reality to be *very useful*
- Compartments may or may not have *physical meaning*
- The compartment model involves *parameters* that *quantify* how the processes of *absorption*, *distribution*, and *elimination* (*metabolism* and *excretion*) take place

2. What is Pharmacokinetics?

One-compartment model with first-order absorption, elimination:



$$\begin{aligned}\frac{dX(t)}{dt} &= k_a X_a(t) - k_e X(t), & X(0) &= 0 \\ \frac{dX_a(t)}{dt} &= -k_a X_a(t), & X_a(0) &= D\end{aligned}$$

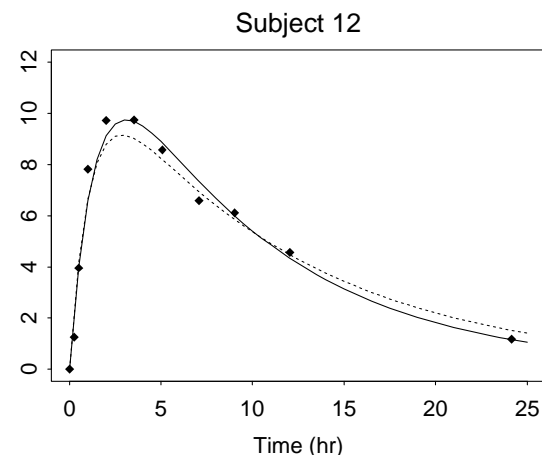
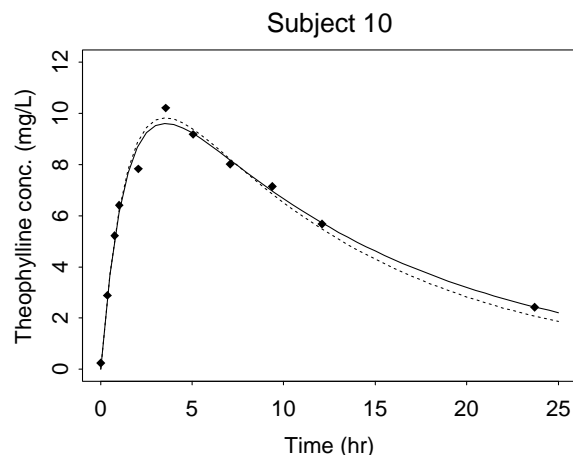
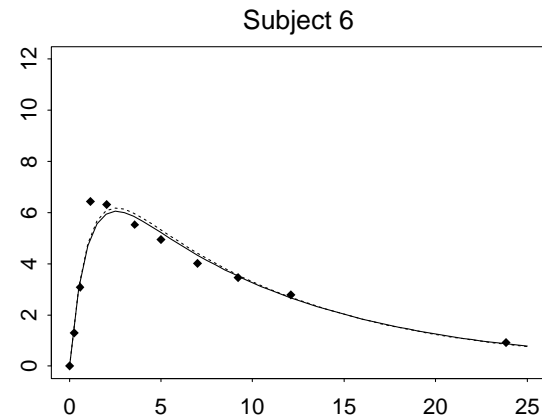
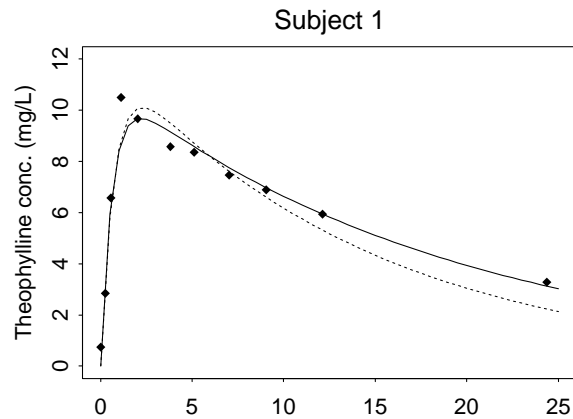
$X_a(t)$ = amount at absorption site

$$C(t) = \frac{X(t)}{V} = \frac{k_a D}{V(k_a - k_e)} \{ \exp(-k_e t) - \exp(-k_a t) \}, \quad k_e = Cl/V$$

k_a = *absorption rate*, V = "*volume*" of compartment, Cl = *clearance*

2. What is Pharmacokinetics?

$C(t)$ “fits” pretty well!



2. What is Pharmacokinetics?

Fancier models are possible:

- *More* compartments (e.g. peripheral tissues, organs),
- *Physiologically-Based Pharmacokinetic* (PBPK) models

Result: *Mathematical model* for time-concentration *within a subject*

- Depends on *PK parameters* characterizing *ADME* processes *for that subject* (k_a, V, Cl)
- If we knew the *PK parameters*, we could *predict* the concentration that would be achieved by the subject at *any time* following *any dose*
- *Multiple doses*: Apply the *principle of superposition*
- \implies Can develop *dosing regimens* and identify those that keep concentrations in the *therapeutic window*

2. What is Pharmacokinetics?

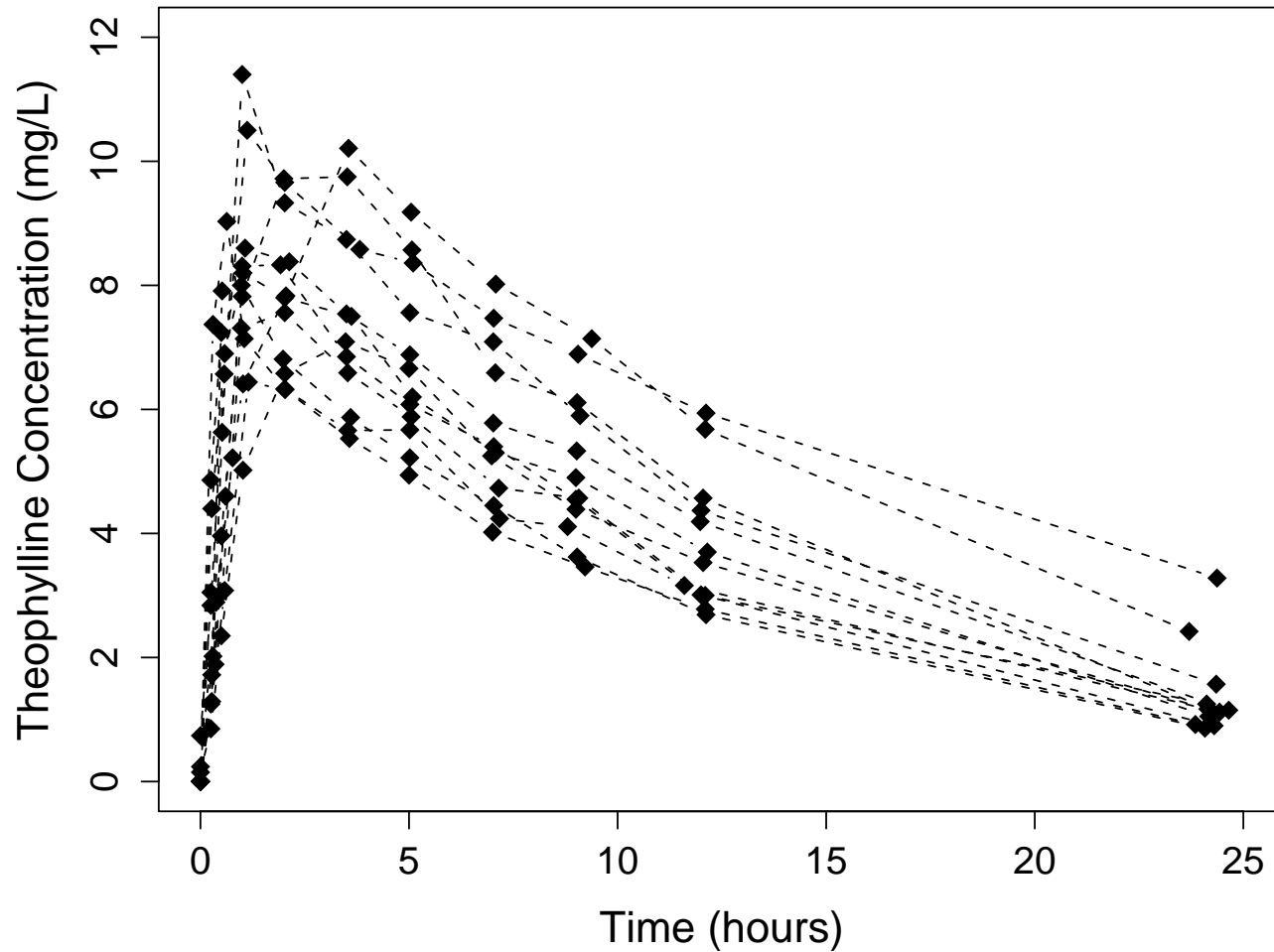
Complication: There is substantial *variation* in ADME across people

- *Identical dose* \implies *variation* in drug concentrations among people. . .
- . . . attributed to *variation* in ADME among people
- If we are going to make *dosing recommendations* suitable for the *whole population*, we need to understand *variation in ADME*!
- If it is *large* \implies hard to make “*one-size-fits-all*” recommendations!
- If some of the variation is *systematically associated* with *subject characteristics* like weight, age, kidney function, smoking behavior, etc., can develop *tailored recommendations* for *subpopulations* of subjects sharing the same characteristics.

Needed: A *formal framework* in which to *describe and study* variation in ADME! *Stay tuned. . .*

2. What is Pharmacokinetics?

All subjects in the theophylline study:



3. What is Pharmacodynamics?

Only half the battle!

- What is a “*good*” drug concentration?
- What is the “*therapeutic window*?” Is it *wide* or *narrow*? Is it the same for *everyone*?

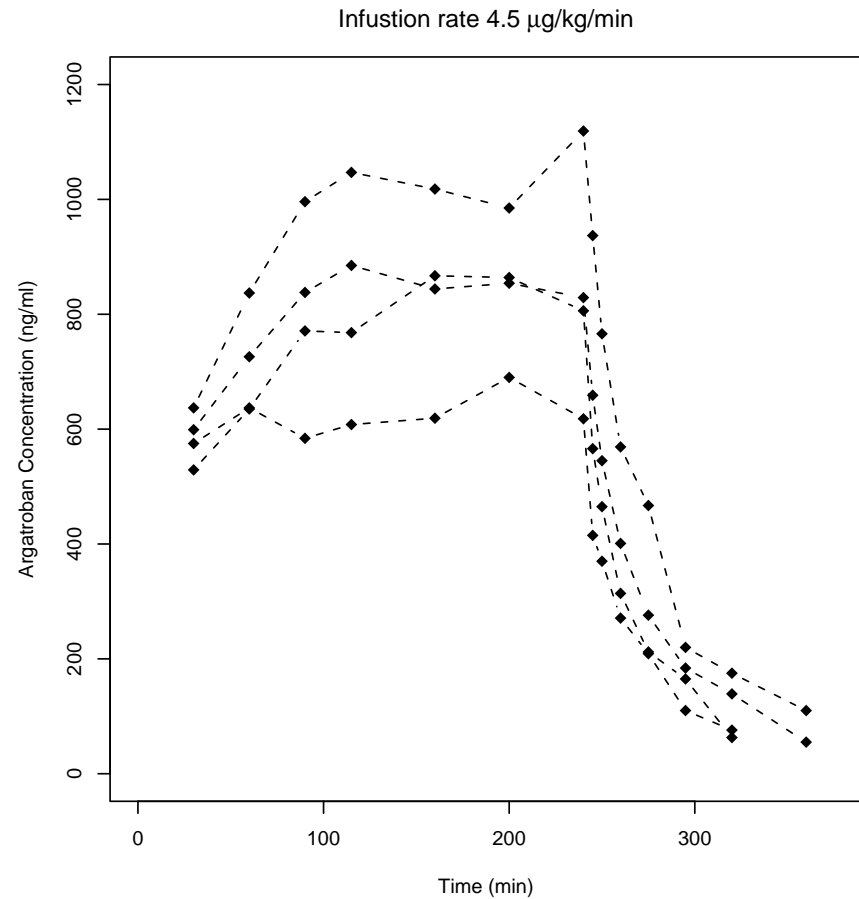
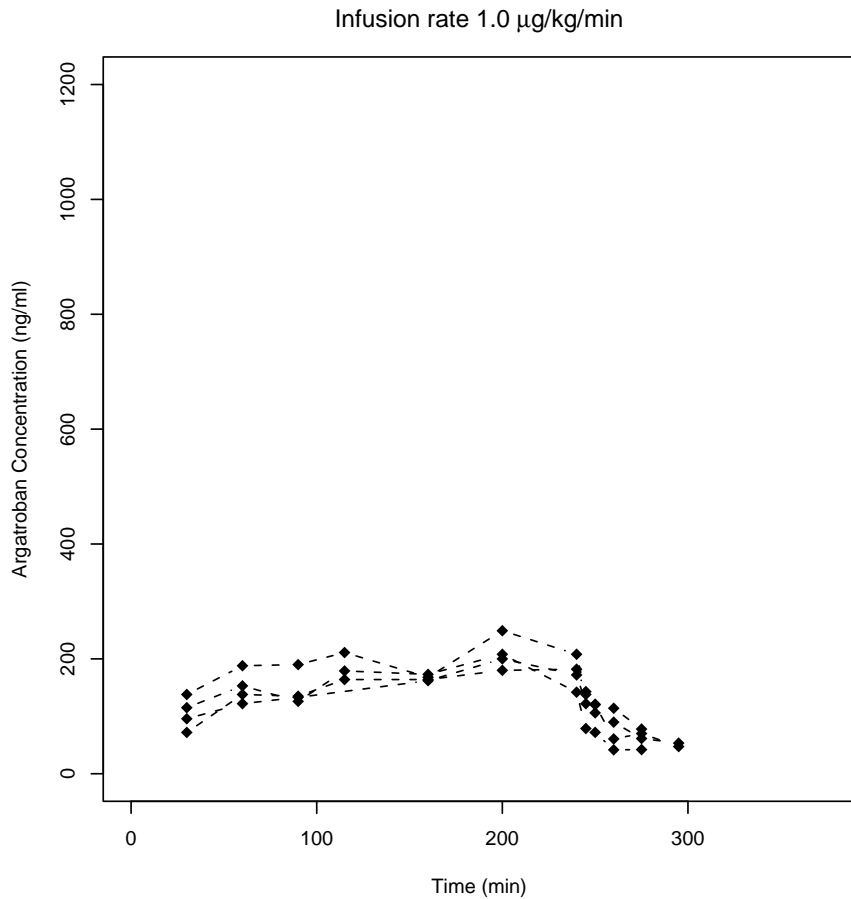
Pharmacodynamics: Relationship of *response* to drug *concentration*

“**What the drug does to the body**”

PK/PD study: Collect *response* data from each subject, too!

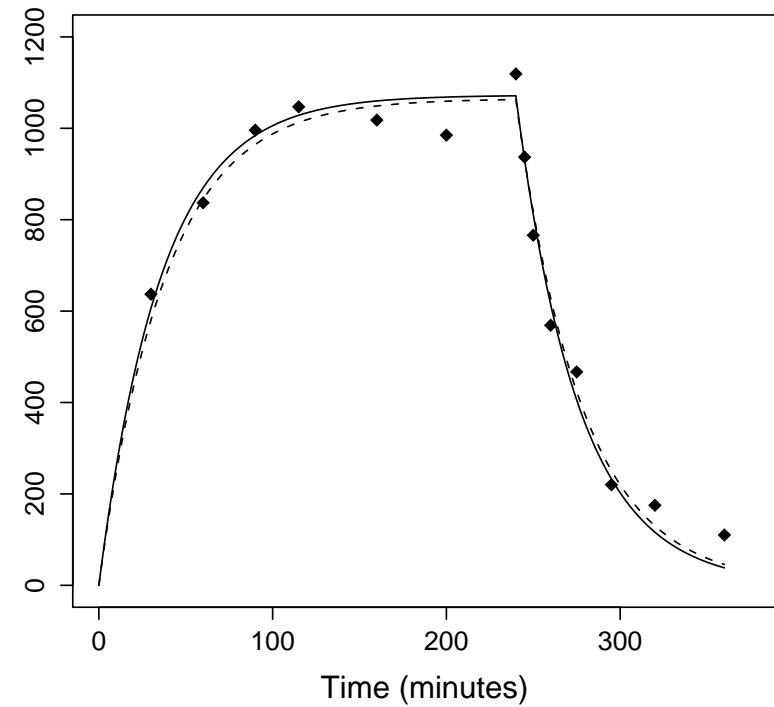
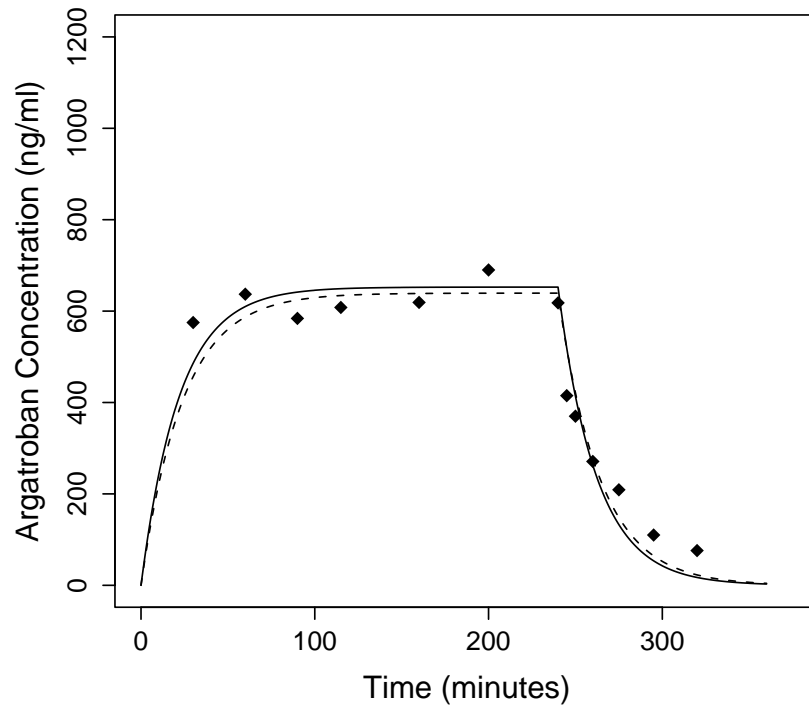
3. What is Pharmacodynamics?

Anticoagulant study: Intravenous infusion PK data



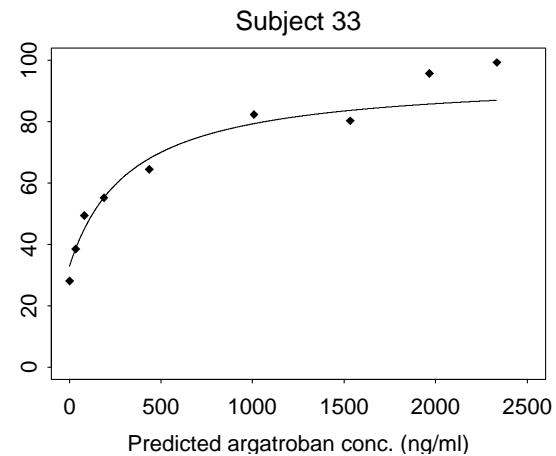
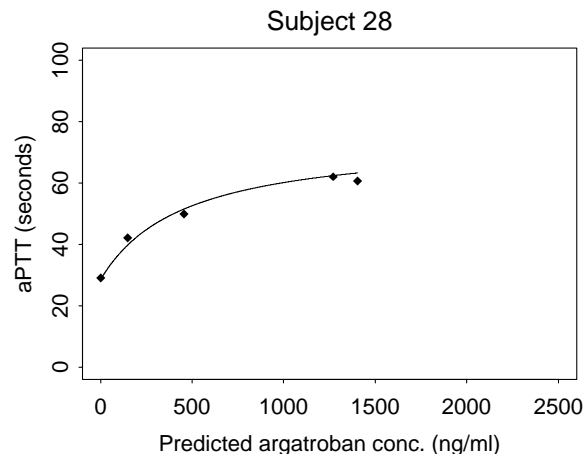
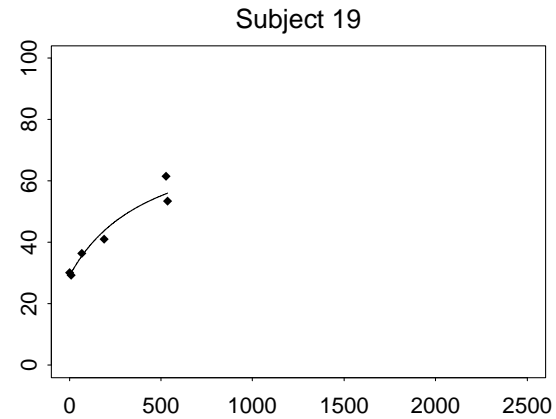
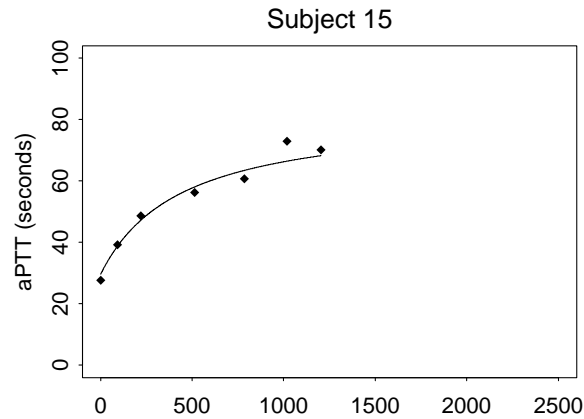
3. What is Pharmacodynamics?

Anticoagulant study: “Fits” of PK model for two subjects



3. What is Pharmacodynamics?

Anticoagulant study: *Concentration-response* for 4 subjects



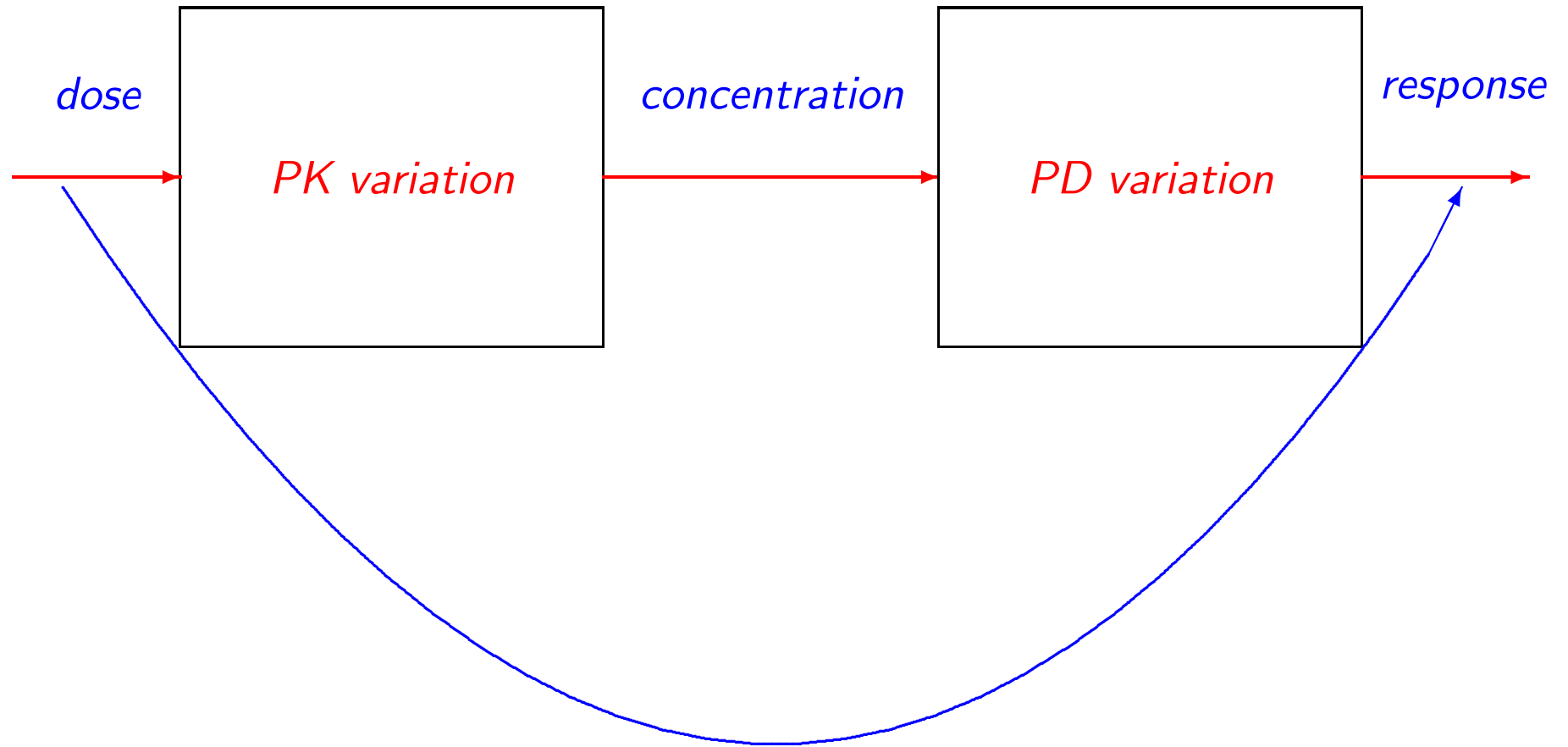
3. What is Pharmacodynamics?

Pharmacodynamics: Study concentration-response *within subjects* and how it *varies* across subjects

- Could just look at the relationship between *dose* and *response*
- But subjects who receive the *same dose* can achieve *very different concentrations*
- And, *likewise*, subjects who achieve the *same concentrations* can show *very different responses*!
- \implies Understanding *concentration-response* for *individuals* provides more precise information
- ...and gives information on the *therapeutic window*

Needed: A *formal framework* to relate ADME leading to concentrations to responses!

3. What is Pharmacodynamics?



4. Population PK/PD and Statistics

How to do all of this? *Statistics to the rescue!*

- Use a *statistical model* for data in PK and PK/PD studies
 - PK: *time-concentration* data
 - PD: *response* data
- Plus *subject characteristics* that could explain the some of the *variation*

For brevity: Focus on PK only

- *Premise of the PK model:* Each subject may “follow” the *same compartment model* but with his or her *own PK parameters* which in turn *vary* across subjects

“Population PK and PK/PD”: Studies and analyses of them based on this type of *statistical model*

4. Population PK/PD and Statistics

Statistical model for PK: N subjects, $i = 1, \dots, N$

- For subject i : “*Subject-specific*” (k_a, V, Cl)

$$C_i(t) = \frac{k_{ai}D}{V(k_{ai} - k_{ei})} \{ \exp(-k_{ei}t) - \exp(-k_{ai}t) \}, \quad k_e = Cl_i/V_i$$

- *Data*: Concentrations C_{ij} at times t_{ij} (*measurement error*)

$$C_{ij} = C_i(t_{ij}) + e_{ij}$$

- (k_{ai}, V_i, Cl_i) take their values across i as described by a *probability distribution*
- Can build in *relationship* between (k_{ai}, V_i, Cl_i) values and *subject characteristics*
- *Nonlinear mixed effects model*

4. Population PK/PD and Statistics

Implementation: For PK

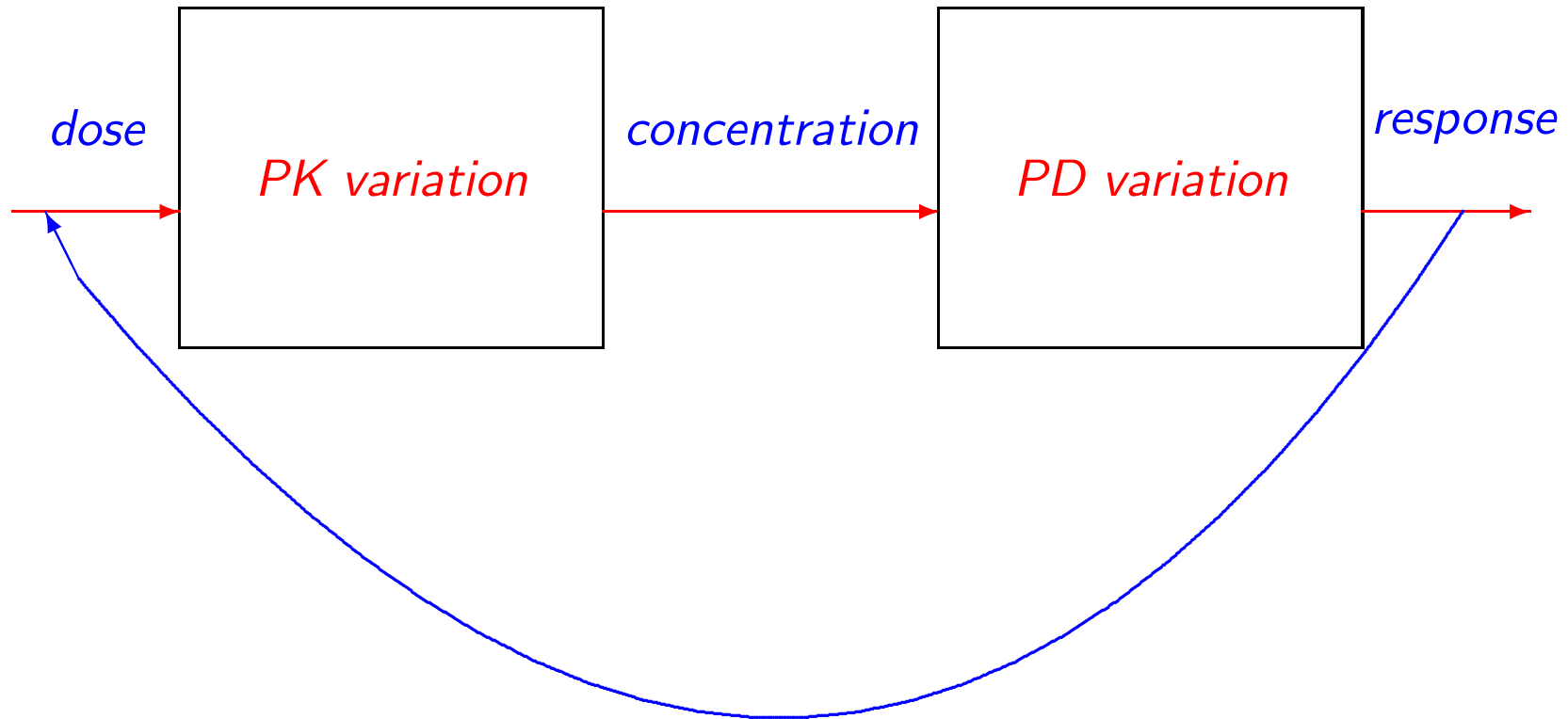
- “*Fit*” this *statistical model* to the data from the *sample* of subjects using sophisticated statistical techniques to *quantify*
 - *average PK parameters* (ADME)
 - the extent of *variation* in PK parameters
 - relationships of PK parameters to *subject characteristics*
- Use this knowledge to develop *dosing recommendations* for the *entire population*
- ... and, if necessary, for *subpopulations* with certain characteristics (e.g., the elderly)

For PK/PD: Add another part to the model relating $C_i(t)$ to $R_i(t) =$ *response* model for subject i

4. Population PK/PD and Statistics

Ultimate objectives:

- Improve the *drug development* process (choose “*good*” doses to take forward to *pivotal* studies of the drug)
- Inform better drug use in *routine clinical care*



4. Population PK/PD and Statistics

Guidance for Industry Population Pharmacokinetics

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

February 1999
CP 1

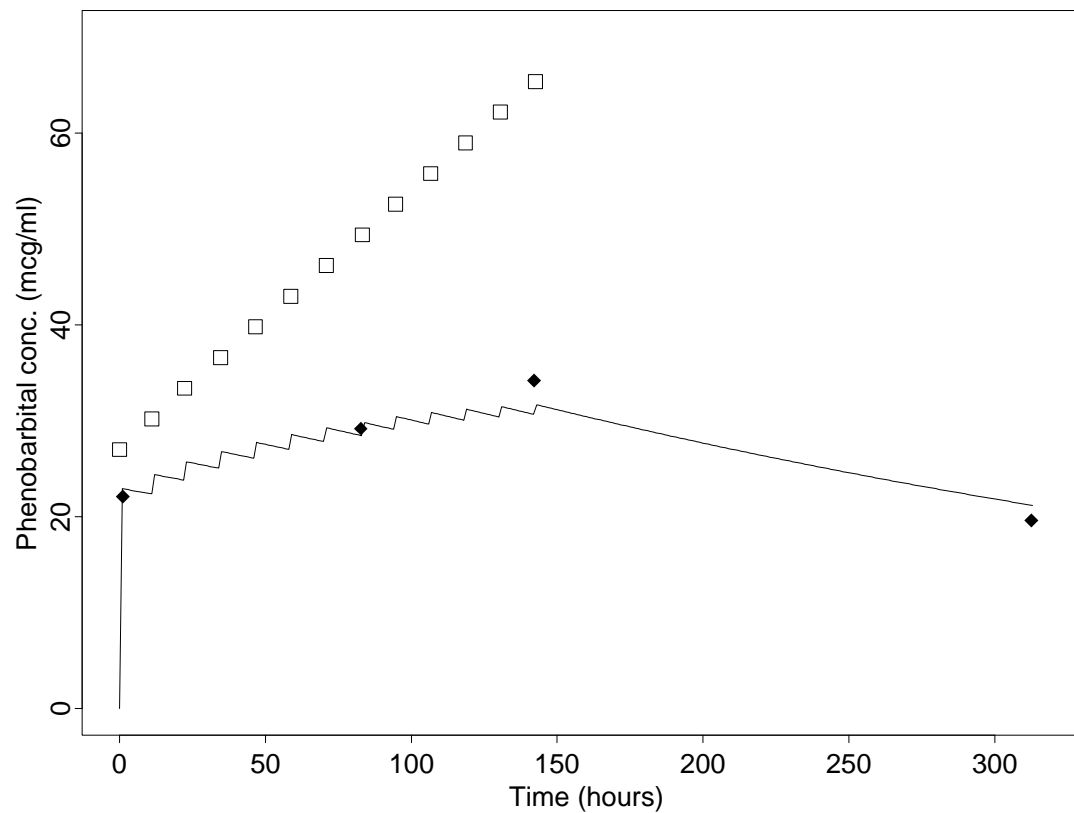
4. Population PK/PD and Statistics

Current interest:

- FDA Advisory Committee for Pharmaceutical Science and Clinical Pharmacology
- Incorporation of *genetic/genomic characteristics*
- Special considerations for *pediatric populations*
- *Clinical trial simulation*

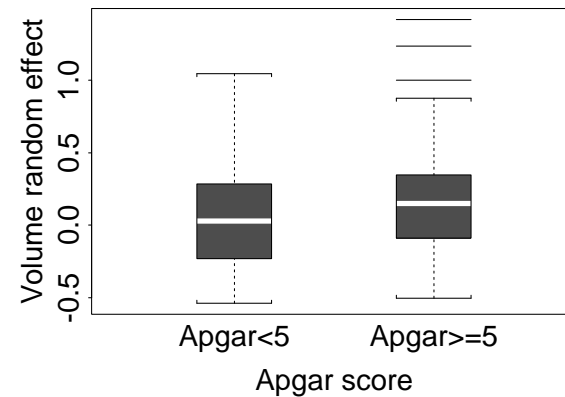
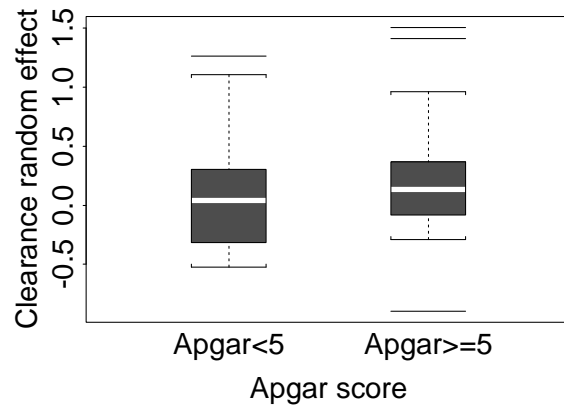
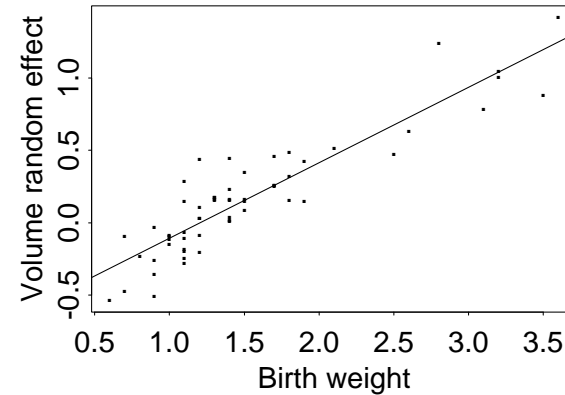
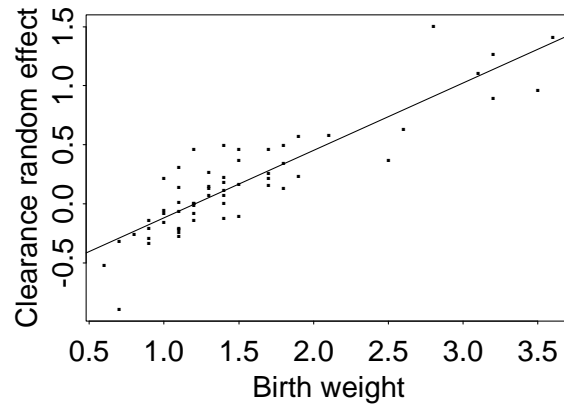
4. Population PK/PD and Statistics

Population PK study of phenobarbital in pre-term infants: *Dosing history* and *concentrations* for one infant



4. Population PK/PD and Statistics

Infant-specific clearance and volume vs. infant characteristics:



5. Concluding Remarks

The next time you take a drug:

- The *dosing recommendations* on the label were probably established through *population PK/PD studies*...
- ...and *statistical modeling* played a central role!

5. Concluding Remarks

Where to find a great intro course on PK on the web:

<http://www.boomer.org/c/p1/>

Thanks to David Bourne at University of Oklahoma for some of the pictures in this talk!

Some books about PK/PD:

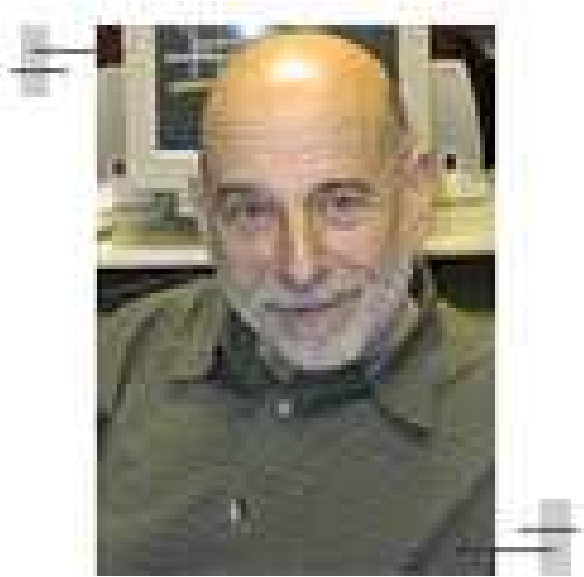
Rowland, M. and Tozer, T.N., *Clinical Pharmacokinetics: Concepts and Applications* (*n*th edition)

Gibaldi, M. and Perrier, D., *Pharmacokinetics* (2nd edition)

Journal with lots of statistical content: *Journal of Pharmacokinetics and Pharmacodynamics* (formerly *Journal of Pharmacokinetics and Biopharmaceutics*)

Dedication

This lecture is dedicated to the memory of



Lewis B. Sheiner, M.D.
1940–2004