<table>
<thead>
<tr>
<th>Date</th>
<th>Topic</th>
<th>Presenter</th>
</tr>
</thead>
<tbody>
<tr>
<td>4/3/2013</td>
<td>Pharmacokinetics and Pharmacodynamics</td>
<td>Elliot Landaw, MD, PhD</td>
</tr>
<tr>
<td>4/10/2013</td>
<td>Clinical Pharmacology of Narcotics</td>
<td>Michael Ferrante, MD</td>
</tr>
<tr>
<td>4/17/2013</td>
<td>Biomarkers for Early Detection, and Molecular Targeting of Putative Markers, for Ovarian Cancers</td>
<td>Robin Farias-Eisner, MD, PhD</td>
</tr>
<tr>
<td>4/24/2013</td>
<td>Studying Tissue Pharmacokinetics by PET Assessment of Tumor Response to Chemotherapy</td>
<td>Caius Radu, MD</td>
</tr>
<tr>
<td>5/1/2013</td>
<td>Essentials of Geriatric Psychopharmacology</td>
<td>Helen Lavretsky, MD</td>
</tr>
<tr>
<td>5/8/2013</td>
<td>Changes in Pharmacokinetics and Pharmacodynamics During Pregnancy</td>
<td>Carla Janzen, MD, PhD</td>
</tr>
<tr>
<td>5/15/2013</td>
<td>Pharmacokinetics and Pharmacodynamics in Renal Failure</td>
<td>Anjay Rastogi, MD</td>
</tr>
<tr>
<td>5/22/2013</td>
<td>Gene Therapy Approaches to Cancer Treatment</td>
<td>Richard Koya, MD</td>
</tr>
<tr>
<td>5/29/2013</td>
<td>Drug Therapy in Newborns: Peri- and Postnatal HIV treatment</td>
<td>Yvonne Bryson, MD</td>
</tr>
</tbody>
</table>
Pharmacokinetics & Pharmacodynamics

- **Basic Concepts**
- **Issues in Pharmacokinetics (PK)**
  - Clearance
  - Half-lives and Residence Times
  - Distribution Volumes
  - Absorption & Bioavailability Measures
- **Pharmacodynamics (PD)**
  - Steady State Models
  - Linking of PK & PD
Some Resources

- **Texts**
  - M Rowland & RN Tozer  *Clinical Pharmacokinetics*  4th ed., Lippincott Williams & Wilkins 2011

- **Web sites**
  - [www.cc.nih.gov/training/training/principles.html](http://www.cc.nih.gov/training/training/principles.html)
  - [www.pharmpk.com/](http://www.pharmpk.com/)  (links to PK/PD resources)

- **Journals:**
  - *Clinical Pharmacology & Therapeutics*  (www.ascpt.org)
  - *J. Pharmacokinetics & Pharmacodynamics*
Basic - Definitions

- Pharmacokinetics (PK) – quantitative analysis of the kinetics (time course) and steady state (SS) relationships of drug

  "What the body does to the drug"

  "ADME"

  - Absorption
  - Distribution
  - Metabolism
  - Excretion

  Elimination
Basic - Definitions

- Pharmacodynamics (PD) – quantitative analysis of relation of drug concentration at an effect site ($C_e$) to drug effect ($E$).

  “What the drug does to the body”

- Understand Dose-Effect relationships

- SS: $C_e \propto$ measured plasma concentration

- Non-SS: may need to use PK to infer $C_e$
PATIENT CHARACTERISTICS IMPACT DRUG RESPONSE

PHARMACEUTICAL PHASE

PHARMACOKINETIC PHASE

PHARMACODYNAMIC PHASE

DOSE

DISINTEGRATION OF FORMULATION
DRUG DISSOLUTION

Dosing Regimen
dose, frequency, route

EFFECT Site Concentrations
DRUG-TARGET RECEPTOR INTERACTION

Effect

Effect Site Concentrations

Concentrations

Plasma, urine, tissue, ...

Parent and metabolites

EFFECTS

Rx, Toxic

source: A. Atkinson
Steady State vs. Kinetic Studies

- Steady state (SS) with constant IV infusion
  - conc. **not** changing with time
  - plasma conc. $C_{SS}$ reflects $C_{tissue}$ (usually)
  - PK (+load) determine time until ~SS

- SS from Repetitive dosing (oral, IM, etc.)
  - eventually reach constant “Profile SS”
  - $C_{max} = \text{peak}$ ; $C_{min} = \text{trough}$ ; average $C_{SS}$
Repetitive Dosing and “Profile SS”

source: Rowland & Tozer
Steady State vs. Kinetic Studies

- Many PK/PD concepts are for SS
  - Clearance; Volume of distribution
  - SS PD effect for given SS conc.
  (time to PD SS may be longer than time to plasma SS)

- But some studies are kinetic
  - e.g., single oral dose or I.V. bolus
  - Tracer kinetic studies; PET
  - Aim may be infer SS under rep. dosing
Linear vs Nonlinear System

“Linear Pharmacokinetics”

- double the dose $\Rightarrow$ concentration doubles
  - **AUC proportional to dose**

- **Superposition principle (example):**
  
  If $\{I.V. \text{ bolus}\} \Rightarrow C_{iv}(t)$ and $\{\text{oral dose}\} \Rightarrow C_{oral}(t)$,
  
  then $\{\text{both dosing together}\} \Rightarrow$

  $$C(t) \equiv C_{iv}(t) + C_{oral}(t)$$

- holds for small enough doses (microdoses)

- linearity for large doses if transport, binding, and elimination remain first order
The relationship between the AUC of (+)-methylphenidate and dose following oral administration of 10, 20, 30, and 40 mg of the racemate to the same volunteer. No appreciable difference is seen for the metabolites. (From: Aoyama T, Kotaki H, Sasaki T. Nonlinear kinetics of threo-methylphenidate enantiomers in a patient with narcolepsy and in healthy volunteers. Eur J Clin Pharmacol 1993;44:79–84.)
Linear vs Nonlinear System

- single kinetic study + linearity $\Rightarrow$ can predict response to any input, including getting to SS

- but for NONlinear systems:
  - CL, V, etc. not constant; depend on $C_{SS}$, Dose
  - requires testing at different doses; models
  - time to SS not predicted by single dose study

- Common nonlinearities
  - Saturation kinetics (Michaelis-Menten)
  - Saturable plasma protein, tissue binding
  - Threshold effects (e.g., glucose spilling)
  - Induction; Neuro./hormonal regulation
Importance of Experiment Design

- Quality & interpretation of PK/PD data depend critically on design:
  - Dose(s), route, and form (bolus vs infusion)
  - What to sample
    - Plasma, urine, tissue, PET, …
    - Total vs. unbound concentrations
    - Parent compound, metabolites
    - PD Effect measures
  - What times to sample in a kinetic study

- Train team: record what was done, not just asked
Pharmacokinetics & Pharmacodynamics

- **Basic Concepts**

- **Issues in Pharmacokinetics (PK)**
  - Clearance
  - Half-lives and Residence Times
  - Distribution Volumes
  - Absorption & Bioavailability Measures

- **Pharmacodynamics (PD)**
  - Steady State Models
  - Linking of PK & PD
Organ Clearance

- **Physiology:** organ clearance as SS concept

  - **"E"** = Single pass extraction fraction:
    \[ E = \frac{\text{Elim. flux}}{\text{input flux}} = \frac{C_{B_{\text{art}}} - C_{B_{\text{ven}}}}{C_{B_{\text{art}}}} \]

  - Clearance ≡ Elim. flux / C_ref (vol/time)
    
    - If use \( C_{B_{\text{art}}} \) as \( C_{\text{ref}} \), Clearance = \( E \times Q \)

\[ \text{Elim. Flux} = Q(C_{B_{\text{art}}} - C_{B_{\text{ven}}}) \quad (\text{mass/time}) \]
Organ Clearance

- Clearance $\equiv \text{Elim. flux}/C_{\text{ref}}$
  - Elimination (metabolism, transport) often function of unbound $C_u$ (free plasma fraction)
  - $C_u = f_u C$ (but $f_u$ not routine measurement)

- Clearance $= E \times Q$
  - high $E$ ($E>0.7$), CL sensitive to $\Delta Q$, not $\Delta f_u$
  - low $E$ ($E<0.3$) $\downarrow Q \implies \uparrow$ transit time $\implies \uparrow E$
    CL sensitive to $\Delta f_u$, CYP induction or inhibition
    but SS “exposure” $= f_u AUC$ not sensitive to $\Delta f_u$
Renal Clearance (CL$_R$)

- Easiest organ CL to measure
  
e.g.
  
  $$\text{Net CL}_R = \frac{\text{urine exc. rate}}{\text{mid-collection C}}$$

- Elim. flux = filtration + secretion – reabs.

- GFR $\approx$ CL$_{\text{creat}} = 120$ ml plasma water/minute

- CL$_R$ due just to filtration $=$ GFR$\times f_u$
Total Clearance (CL_T or just CL)

- SS Clearances add:
  \[
  CL = CL_R + CL_H + \text{nonrenal/nonhepatic clearance}
  \]

- Estimating CL from single dose kinetic study
  - i.v. Dose: \[
  CL = \frac{\text{Dose}}{\int_0^\infty C(t)\,dt} = \frac{\text{Dose}}{\text{AUC}}
  \]
  - Oral Dose: \[
  CL = F \times \frac{\text{Oral Dose}}{\text{AUC}}
  \]
  where \( F \) = fraction of dose reaching “central pool”
  (plasma + tissue in rapid equilibrium with plasma)

- \[
  CL_{\text{oral}} \equiv \frac{CL}{F} = \frac{\text{Oral Dose}}{\text{AUC}}
  \]
Estimating AUC

- **Trapezoidal rule:**
  
  Fit model of data to entire $C(t)$. e.g.,
  
  $$C(t) = A_1 \exp(-\lambda_1 t) + \ldots + A_n \exp(-\lambda_n t)$$
  
  $$\text{AUC} = \frac{A_1}{\lambda_1} + \ldots + \frac{A_n}{\lambda_n}$$

- **Fit model of data** to entire $C(t)$. e.g.,
  
  May need to fit single exponential at end to estimate tail area to $\infty$
Using Profile SS to estimate AUC

Profile SS after multiple repeated doses:

use area under one cycle to estimate single dose AUC

single dose AUC (from 0 to ∞)

source: Rowland & Tozer
Predicting SS Concentration #1

- **Constant i.v. flux infusion** $I$ (mass/time)
- SS plasma conc. $\equiv C_{SS} = C(\infty)$
- total CL = (total Elim. Flux)/$C_{ref}$

  - Here $C_{ref}$ is $C_{SS}$
  - Since patient at steady state, Elim. Flux = $I$

Therefore, $C_{SS} = I / CL$
Predicting SS Concentration #2

For repetitive oral dose $D$ every $T$ units of time, at Profile Steady State:

$$\text{average } C_{SS} = \frac{(FD/T)}{CL} .$$

i.e. $$\text{average } C_{SS} = \frac{(D/T)}{CL_{oral}}$$

where $CL_{oral}$ estimated from kinetic study by

$$CL_{oral} = \frac{\text{Oral Dose/AUC}}{F} = CL/F$$
Half-lives and Residence Times

- 1-compartment approximation for body:
  - Drug distributes in **single**, well-mixed central pool
  - 1st order elimination rate \( k \) (time\(^{-1}\)); volume \( V \)

\[
V = \frac{Dose}{C(0)}
\]

\[
t_{1/2} = \frac{0.693}{k} \quad \text{(half-life of drug in whole body)}
\]

\[
MRT = \frac{1}{k} \quad \text{(Mean Residence Time in body)}
\]

\[
V = \text{total drug distribution volume} = \text{CL} \times \text{MRT}
\]

\[
C(t) = \left(\frac{Dose}{V}\right)\exp(-kt)
\]

\[
\log C(t)
\]
"Is this single exponential decay?"

"What's the half-life of this drug?"
conc. on LOG scale suggests “No!”

initial $t_{1/2}$ 0.6 hours

terminal $t_{1/2}$ 14 hours
Half-lives and Residence Times

- multi-compartment approximation for body:
  - Drug distributes in central + peripheral pool(s)
  - $C(t)$ exhibits elimination and distribution kinetics

$$C(t) = A_1 \exp(-\lambda_1 t) + A_2 \exp(-\lambda_2 t)$$

- 2 or more “half-lives,” but terminal half-life not always the main factor for dosing, accumulation, etc.
- Relative importance each half-life depends on $A_i/\lambda_i$
Caution: Interpreting Terminal $t_{1/2}$

- Terminal $t_{1/2}$ often rate limited by elimination
- BUT NOT ALWAYS!
- counterexample: gentamicin
  - $CL_{cr} \ 6 - 107$ ml/min
  - terminal $t_{1/2}$ in all $\sim 90$ hrs
  - renal impairment affects mainly first half-life
  - avg $C_{SS}$ still $(D/T)/CL_{oral}$
  - but dosing interval $T$ to achieve desired $C_{max}/C_{min}$
    trickier to compute

source: Rowland & Tozer  Schentag et al.  JAMA 238:327-9, 1977
Mean Residence Time (MRT)

- MRT = mean time molecule of drug resides in body before being irreversibly eliminated

- Assumes linear system

- May be useful summary measure when there are multiple half-lives

- Effective (overall) half-life = $0.693 \times \text{MRT}$
Mean Residence Time

- MRT estimated from a kinetic study:

  Measure plasma concentration $C(t)$ after dose:

  $$\text{MRT} \geq \frac{\text{AUMC}}{\text{AUC}} \equiv \frac{\int_0^\infty tC(t)dt}{\text{AUC}}$$

- MRT = AUMC/AUC requires

  - no “peripheral” elimination
  - no traps
  - linear PK
Mean Residence Time

- **1-compartment model**
  - $MRT = \frac{1}{k} = \frac{V_1}{CL}$
  - half-life = $0.693 \times MRT$
  - time to reach 90% SS following constant flux infusion is 2.3 MRT’s = 3.3 half-lives

- **Multi-exponential model**
  - $\frac{AUMC}{AUC} = \frac{w_1}{\lambda_1} + \ldots + \frac{w_n}{\lambda_n}$
    where $w_i \propto \left( \frac{A_i}{\lambda_i} \right)$ and $w_1 + \ldots + w_n = 1$
  - 2.3 MRT’s (i.e., 3.3 effective half-lives) is time to reach at least 84% SS
Distribution Volumes

Volume of Central Pool ($V_1$)

- $V_1 = \text{i.v. Dose}/C(0)$
- $C(0)$ estimated by back-extrapolating from early concentrations
- $V_1 = \text{plasma + tissues in rapid equilibrium by time of earliest plasma sample}$
- determines (transient) peak plasma concentration following i.v. dose
multi-compartment approximation for body:
- Drug distributes in central + peripheral pool(s)
- $C(t)$ exhibits elimination and distribution kinetics

$\log C(t)$

$C(t) = A_1 \exp(-\lambda_1 t) + A_2 \exp(-\lambda_2 t)$

- Back-extrapolated $C(0) = A_1 + A_2$
- $V_1 = \text{Dose} / C(0)$
SS **Total Distribution Volume**

\( (V_{SS}, V_D \text{ or just } V) \)

- Assume at SS
- \( A(\infty) = \text{total amount of drug in body at SS} \)
- Define \( V = A(\infty) / C_{SS} \)

  Hypothetical volume SS mass would have to occupy to yield same concentration as \( C_{SS} \)

\[ V = CL \times MRT \]

- Provides insights into distribution, permeation, tissue binding, etc.
- back-extrapolated \( C(0) \) from **terminal** decay (i.e., \( V_{\text{extrap}} \)) may overestimate \( V \)
$t_{1/2}$ depends on CL and V.
Absorption & Bioavailability

FACTORS AFFECTING RATE AND EXTENT OF DRUG ABSORPTION

source: A. Atkinson
Bioavailability

- Measures of extent and rate of absorption from admin. site to measurement site (latter usually central pool, i.e. plasma)
- i.v. administration is “gold standard” for complete and instantaneous absorption
- single oral dose: “informal” measures are:

\[
C_{\text{peak}} \quad t_{\text{peak}}
\]
Bioavailability – formal measures

“F” estimates extent of absorption
- Separate i.v. and oral studies
- \[ F = \left( \frac{\text{Dose}_{\text{iv}}}{\text{Dose}_{\text{oral}}} \right) \times \frac{\text{AUC}_{\text{oral}}}{\text{AUC}_{\text{iv}}} \]
  fraction of administered dose reaching plasma

MAT (mean absorption time)
- \[ \frac{\text{AUMC}_{\text{oral}}}{\text{AUC}_{\text{oral}}} - \frac{\text{AUMC}_{\text{iv}}}{\text{AUC}_{\text{iv}}} \]

Absorption rate constant (compartmental model)

Absorption flux time course (deconvolution)
Example: Rifampicin pretreatment reduces oral digoxin bioavailability.

**FIGURE 7-4.** Rifampicin pretreatment reduces the absorption of digoxin. Shown are plots of mean plasma digoxin concentration–time profiles after oral and i.v. administration (as a 30-min infusion) of 1 mg digoxin alone (●) and after 10 days rifampicin pretreatment (600 mg daily, ●) to seven healthy adults. A clear depression in the oral absorption of digoxin is inferred by the lower concentrations after oral but not i.v. administration after rifampicin pretreatment. This was corroborated by a 30% decrease in total AUC(0–144hr) (from 54.8 to 38.2 μg-hr/L), corresponding to a fall from 63% to 38% in oral bioavailability. (From: Greiner B, Eichelbaum M, Fritz P, et al. The role of intestinal P-glycoprotein in the interaction of digoxin and rifampin. J Clin Invest 1999;104:147–153.)
Pharmacokinetics & Pharmacodynamics

- Basic Concepts
- Issues in Pharmacokinetics (PK)
  - Clearance
  - Half-lives and Residence Times
  - Distribution Volumes
  - Absorption & Bioavailability Measures
- Pharmacodynamics (PD)
  - Steady State Models
  - Linking of PK & PD
Dose-Effect Relationships

**Drug Dose**

- C(t)
- PD
- Effect(s)

**PK**

**Covariates**

- age
- sex
- body size
- organ function
- disease
- other drugs
- genes/markers
Simplest PD Model: Binary, 2-State

Graded Effect $\propto 1^0$ Drug-Receptor complex

Effect = \frac{\text{Maximal effect} \cdot [\text{Drug}]}{K_D + [\text{Drug}]}

(K_D = k_2/k_1)

source: Frank M. Balis
Graded Dose-Effect Curve

Maximal effect (efficacy)

% of Maximal Effect

EC\textsubscript{50}

[Drug]
Comparing Dose-Effect Curves

\[ \text{Effect} = \frac{\text{Maximal effect} \cdot [\text{Drug}]}{K_D + [\text{Drug}]} \]
Empirical Pharmacodynamic Models

- Fixed effect model
- Linear model
- Log-linear model
- $E_{\text{max}}$ model
- Sigmoid $E_{\text{max}}$ model

Effect equations:

- Linear model: $\text{Effect} = E_0 + S \cdot [\text{Drug}]$
- Log-linear model: $\text{Effect} = I + S \cdot \log([\text{Drug}])$
- $E_{\text{max}}$ model: $\text{Effect} = \frac{E_{\text{max}} \cdot [\text{Drug}]^H}{EC_{50}^H + [\text{Drug}]^H}$
Sigmoid $E_{\text{max}}$ PD Model

Effect (%)

- $H = 5$
- $H = 2$
- $H = 1$
- $H = 0.5$
- $H = 0.1$

Effect (%)

- $EC_{50}$

[Drug]

source: Frank M. Balis
Hysteresis and Proteresis Loops

- Equilibration delay in plasma and effect site conc.
- Formation of active metabolite
- Receptor up-regulation

- Tolerance
- Receptor tachyphylaxis
PK/PD Applications

- **Drug discovery/development**
  - Scaling (cell culture ⇒ animal ⇒ human)
  - Feasible dosing, drug delivery
  - Predict and quantify inter- & intra-patient variability
  - Regulatory issues (FDA)

- **Basic and Clinical Sciences**
  - Understand *in vivo* mechanisms
  - Quantify PK and PD study endpoints
  - Design of clinical studies
    - Dosing regimens
    - Timing of samples
    - Identify important covariates
PK/PD Applications

- **Therapy**
  - Optimal treatment strategies
  - Individualization of therapy
  - Clinical monitoring (PD) or predicting (PK/PD) efficacy and toxicity endpoints

- **Pharmacogenetics/pharmacogenomics**
  - Hereditary variations in response (PK or PD)
  - Identification of genes or loci
  - Genome-based drug discovery
  - Predict efficacy and potential adverse effects