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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](http://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

ABSORPTION

DISTRIBUTION

METABOLISM

EXCRETION

Concentrations
Plasma, urine, tissue, ...
Parent and metabolites

Effect Site Concentrations
DRUG-TARGET RECEPTOR INTERACTION

EFFECTS
Rx, Toxic

source: A. Atkinson
Steady State vs. Kinetic Studies

- **Steady state (SS) with constant IV infusion**
  - Concentration *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”
  - $C_{\text{max}} = \text{peak} ; C_{\text{min}} = \text{trough} ; \text{average } C_{SS}$
Repetitive Dosing and “Profile SS”

C<sub>max</sub>

C<sub>min</sub>

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 ⇒ concentration doubles
  - AUC proportional to dose

- Superposition principle (example):
  If {I.V. bolus} ⇒ $C_{iv}(t)$ and {oral dose} ⇒ $C_{oral}(t)$,
  then {both dosing together} ⇒
  $$C(t) \equiv C_{iv}(t) + C_{oral}(t)$$

- 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

  \[ E = \frac{\text{Elim. flux}}{\text{input flux}} = \frac{C_{B_{\text{arterial}}} - C_{B_{\text{venous}}}}{C_{B_{\text{arterial}}}} \]

  \[ \text{Clearance} \equiv \frac{\text{Elim. flux}}{C_{\text{ref}}} \quad (\text{vol/time}) \]

- “E” = Single pass extraction fraction:

  \[ E = \frac{\text{Elim. flux}}{\text{input flux}} = \frac{C_{B_{\text{arterial}}} - C_{B_{\text{venous}}}}{C_{B_{\text{arterial}}}} \]

- **Clearance**

  \[ \text{Clearance} = E \times Q \]

- If use \( C_{B_{\text{arterial}}} \) as \( C_{\text{ref}} \)
Organ Clearance

- Clearance $\equiv$ Elim. flux/$C_{ref}$
  - Elimination (metabolism, transport) often function of unbound $C_u$ (free plasma fraction)
  - $C_u = f_u \times C$ (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 $E$ ($E < 0.3$) $\downarrow Q \Rightarrow \uparrow$ transit time $\Rightarrow \uparrow E$
    - CL sensitive to $\Delta f_u$, CYP induction or inhibition
    - but SS “exposure” = $f_u \times AUC$ 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.

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

- $CL_R$ 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:** \[ CL = \frac{\text{Dose}}{\int_0^\infty C(t)dt} = \text{Dose}/AUC \]
  
  - **Oral Dose:** \[ CL = F \times \frac{\text{Oral Dose}}{AUC} \]
    
    where $F =$ fraction of dose reaching “central pool”
    
    (plasma + tissue in rapid equilibrium with plasma)

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

- **Trapezoidal rule:**

  Fit model of data to entire $C(t)$. e.g.,

  $$C(t) = A_1 \exp(-\lambda_1 t) + \ldots + A_n \exp(-\lambda_n t)$$

  $$\text{AUC} = \frac{A_1}{\lambda_1} + \ldots + \frac{A_n}{\lambda_n}$$

  May need to fit single exponential at end to estimate tail area to $\infty$. 

- **Fit model of data to entire $C(t)$**. e.g.,
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**  \( = \frac{(\text{total Elim. Flux})}{C_{\text{ref}}} \)

  - Here \( C_{\text{ref}} \) is \( C_{SS} \)
  - Since patient at steady state,  \( \text{Elim. Flux} = I \)

- **Therefore,**  \( C_{SS} = \frac{I}{CL} \)
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

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

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

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

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

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

\[ V = \text{total drug distribution volume} = CL \times \text{MRT} \]
"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
  - $\text{CL}_{cr}$ 6 – 107 ml/min
  - terminal $t_{1/2}$ in all $\sim$90 hrs
  - renal impairment affects mainly first half-life
  - avg $C_{SS}$ still $(D/T)/\text{CL}_{oral}$
  - 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
  - $\text{MRT} = \frac{1}{k} = \frac{V_1}{\text{CL}}$
  - half-life = $0.693 \times \text{MRT}$
  - time to reach 90% SS following constant flux infusion is 2.3 MRT’s = 3.3 half-lives

- Multi-exponential model
  - $\text{AUMC/AUC} = w_1\left(\frac{1}{\lambda_1}\right) + \ldots + w_n\left(\frac{1}{\lambda_n}\right)$
    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
- $V_1 = \text{plasma} + \text{tissues in rapid equilibrium by time of earliest plasma sample}$
- 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

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

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

($V_{SS}$, $V_D$ or just $V$)

- Assume at SS

- $A(\infty) =$ 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., $V_{extrap}$) may overestimate $V$
\[ t_{1/2} \text{ depends on CL and V} \]
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:

![Graph showing peak concentration (C_peak) and peak time (t_peak).]
Bioavailability – formal measures

■ “F” estimates extent of absorption
  ● Separate i.v. and oral studies
  ● \[ F = \frac{Dose_{iv}}{Dose_{oral}} \times \frac{AUC_{oral}}{AUC_{iv}} \]

  fraction of administered dose reaching plasma

■ MAT (mean absorption time)
  \[ \frac{AUMC_{oral}}{AUC_{oral}} - \frac{AUMC_{iv}}{AUC_{iv}} \]

■ Absorption rate constant (compart. 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 $AUC(0–144\text{hr})$ (from 54.8 to 38.2 $\mu$g·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.)
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Dose-Effect Relationships

Drug Dose

C(t) → PK → PD → Effect(s)

Covariates

- age
- sex
- body size
- organ function
- disease
- other drugs
- genes/markers
Dose-Effect Endpoints

**Graded**
- Continuous scale (dose $\rightarrow$ effect)
- Measured in a single biologic unit
- Relates dose to intensity of effect

**Quantal**
- All-or-none pharmacologic effect
- Population studies
- Relates dose to frequency of effect
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

% of Maximal Effect

Maximal effect (efficacy)

EC$_{50}$

[Drug]

source: Frank M. Balis
Comparing Dose-Effect Curves

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

source: Frank M. Balis
Empirical Pharmacodynamic Models

- **Fixed effect model**

- **Linear model**

- **Log-linear model**

- **$E_{\text{max}}$ model**

- **Sigmoid $E_{\text{max}}$ model**

\[ \text{Effect} = E_0 + S \cdot [\text{Drug}] \]

\[ \text{Effect} = I + S \cdot \log([\text{Drug}]) \]

\[ \text{Effect} = \frac{E_{\text{max}} \cdot [\text{Drug}]^H}{EC_{50}^H + [\text{Drug}]^H} \]
Sigmoid $E_{\text{max}}$ PD Model

Effect (%) vs. [Drug]

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

EC$_{50}$

Source: Frank M. Balis
Concentration and Effect vs. Time

Non-Steady State

- Central Compartment
- Peripheral Compartment
- Effect Compartment

Conc./Amount vs. Time

Effect [% of E_MAX] vs. Time

source: Frank M. Balis
Hysteresis and Proteresis Loops

**Hysteresis Loop** (Counterclockwise)
- Equilibration delay in plasma and effect site conc.
- Formation of active metabolite
- Receptor up-regulation

**Proteresis Loop** (Clockwise)
- 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