USES OF PHARMACOKINETICS

• Basis for *rational dose selection* in therapeutics
• Development and evaluation of new drugs
• Basic studies of *drug distribution* (PET Scan)

TARGET CONCENTRATION STRATEGY

1. Estimate initial dose
2. Target level
3. Loading dose
4. Maintenance dose
5. Begin therapy
6. Assess therapy
7. Patient response
8. Drug level
9. Refine dose estimate
10. Adjust dose
**Rationale for Plasma Level Monitoring**

- Prescribed dose
- Adherence
- Absorption
- Protein bound
- Plasma free
- Elimination
- Metabolism
- Renal excretion
- Distribution
- Biophase receptor binding
- Effect

**First Description of Therapeutic Drug Monitoring**


**Radioimmunoassay**

Rosalyn Sussman Yalow - 1977 Nobel Laureate
DRUG CANDIDATES FOR TDM

- Low therapeutic index
- No physiologic or therapeutic endpoints to guide dosage
- Pharmacokinetics vary widely between individuals
- Need to monitor adherence?

EFFECT OF ADHERENCE RATE ON OUTCOME IN HIV INFECTED PATIENTS


INDICATIONS for Measuring Blood Levels

- To evaluate suspected toxicity
- To evaluate actual or potential lack of therapeutic efficacy
- To monitor prophylactic therapy
- To guide dose adjustment
TARGET CONCENTRATION STRATEGY

ESTIMATE INITIAL DOSE
TARGET LEVEL
LOADING DOSE
MAINTENANCE DOSE

DIGOXIN Levels in TOXIC and NONTOXIC Patients*

* From Smith TW and Haber E. J Clin Invest 1970;49:2377-86.

DIGOXIN: Factors Influencing OUTCOME in “GREY ZONE”

↑ Risk of toxicity in patients with coronary heart disease, hypoxemia, and/or hypokalemia, hypomagnesemia
↓ ECG evidence of toxicity if concurrent therapy with antiarrhythmic drugs
**TRADITIONAL Guidelines for DIGOXIN Levels**

THERAPEUTIC RANGE: 0.8 - 1.6 ng/mL

POSSIBLY TOXIC LEVELS: 1.6 - 3.0 ng/mL

PROBABLY TOXIC LEVELS: > 3.0 ng/mL

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**SURVIVAL as a function of DIGOXIN LEVEL measured after 1 Month Rx**


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**PROPOSED Range of DIGOXIN LEVELS for OPTIMAL THERAPY in CHF**

New Therapeutic Range: 0.5 - 0.9 ng/mL

Benefit results from INHIBITION OF SYMPATHETIC NERVOUS SYSTEM rather than ↑ INOTROPY

BUT DIGOXIN DOSES PRESCRIBED FOR PATIENTS WITH THIS RANGE OF DIGOXIN LEVELS SHOULD HAVE BEEN ASSOCIATED WITH HIGHER LEVELS?
DIGOXIN DOSES for Patients with Levels of 0.5 - 0.8 ng/mL

DIGOXIN DOSE (mg/day)

NUMBER OF PATIENTS

0.125 0.25 0.375 0.50

0 50 100 150 200 250 300 350 400 450


TARGET CONCENTRATION STRATEGY

ESTIMATE INITIAL DOSE
TARGET LEVEL
LOADING DOSE
MAINTENANCE DOSE

BASED ON CONCEPT OF DISTRIBUTION VOLUME

DIGOXIN LEVELS after IV Dose

0.75 mg DIGOXIN IV

TISSUE DIGOXIN
PLASMA DIGOXIN

DISTRIBUTION PHASE | ELIMINATION PHASE
**INITIAL DIGITALIZATION**

Digitalizing dose:

\[ V_d = \frac{750 \times 10^3 \text{ ng}}{1.4 \text{ ng/mL}} = 536 \text{ L} \]

**3 DISTRIBUTION VOLUMES**

\[ V_d (\text{extrap.}) = \frac{\text{DOSE}}{C_0} \]

\[ V_d (\text{area}) = \frac{t_{1/2} \cdot CL}{0.693} \]

\[ V_d (\text{ss}) = V_1 + V_2 + \ldots + V_n \]

**DISTRIBUTION DELAYS ONSET of DIGOXIN Chronotropic Action**

DISTRIBUTION DELAYS ONSET of DIGOXIN Inotropic Action

TARGET CONCENTRATION STRATEGY

ESTIMATE INITIAL DOSE
TARGET LEVEL
LOADING DOSE
MAINTENANCE DOSE

BASED ON CONCEPTS OF ELIMINATION HALF LIFE AND CLEARANCE

ELIMINATION HALF-LIFE

ELIMINATION HALF-LIFE is the TIME REQUIRED FOR THE PLASMA CONCENTRATION (OR TOTAL BODY STORES) OF A DRUG TO FALL TO HALF OF THE CONCENTRATION (OR AMOUNT) PRESENT AT SOME PREVIOUS TIME.
ELIMINATION PARAMETERS

\[ t_{1/2} = \frac{0.693 \cdot V_d}{C_L_E} \]

\[ k = \frac{0.693}{t_{1/2}} \]

\[ C_L_E = k \times V_d \]

\( t_{1/2} = \) elimination half life

\( k = \) elimination rate constant

\( C_L_E = \) elimination clearance

MAINTENANCE DIGOXIN THERAPY

MAINTENANCE DOSE

0.25 mg

NORMAL DAILY LOSS:

= 1/3 Total Body Stores
= 1/3 (0.75 mg)
= 0.25 mg

1.4 ng/mL

DAILY LOSS

0.25 mg

DIGOXIN CUMULATION

.25 x 2/3 = .17
+.25
+.42 x 2/3 = .28
+.25
+.53 x 2/3 = .36
+.25
+.61 x 2/3 = .41
+.25
+.66 x 2/3 = .44
+.25
+.69 x 2/3 = .46
+.25
+.71
CUMULATION FACTOR

\[ CF = \frac{1}{1 - e^{-k\tau}} \]

\( \tau \) = dose interval
\( k \) = elimination rate constant

ELIMINATION RATE CONSTANT

\[ k = \frac{0.693}{t_{1/2}} \]

LOADING & MAINTENANCE DOSES

90% SS in 3.3 x \( t_{1/2} \)
A 39 year-old man with mitral stenosis was hospitalized for mitral valve replacement (October 1981). He had a history of chronic renal failure resulting from interstitial nephritis and was maintained on hemodialysis. His mitral valve was replaced with a prosthesis and digoxin therapy was initiated postoperatively in a dose 0.25 mg/day.

Two weeks later, he was noted to be unusually restless in the evening. The following day, he died shortly after he received his morning digoxin dose. Blood was obtained during an unsuccessful resuscitation attempt, and the measured plasma digoxin concentration was 6.9 ng/mL.
PHARMACOKINETIC ANALYSIS OF DIGOXIN CASE HISTORY

**ESTIMATED T_{1/2}:**
4.3 days \((k = 0.16 \text{ day}^{-1})\)

**TIME TO 90% STEADY STATE:**
3.3 \times 4.3 = 14.2 days

**STEADY STATE PEAK LEVEL:**
6.2 ng/mL \(\text{(post distribution phase)}\)

**MEASURED LEVEL:**
6.9 ng/mL \(\text{(pre distribution)}\)
**STeady State Concentration**

**Continuous Infusion:**

\[ C_{ss} = \frac{I}{CL_E} \]

**Intermittent Dosing:**

\[ \bar{C}_{ss} = \frac{DOSE/\tau}{CL_E} \]

- *Not determined by loading dose*
- *Mean steady state concentration not determined by V_d*
- *Peak and trough are affected by V_d*

**V_d affects peak and trough but not mean levels**

- Graph showing concentration over time with different V_d values.
FOR MOST DRUGS, $C_{ss}$ IS PROPORTIONAL TO DOSE (Dosing Rate)

CONTINUOUS INFUSION:

$C_{ss} = \frac{I}{CL_e}$

INTERMITTENT DOSING:

$\bar{C}_{ss} = \frac{DOSE/\tau}{CL_e}$

STEADY STATE CONCENTRATION

• NOT DETERMINED BY LOADING DOSE
• MEAN STEADY STATE CONCENTRATION NOT DETERMINED BY $V_d$
• CHANGES IN MAINTENANCE DOSE RESULT IN DIRECTLY PROPORTIONAL CHANGES IN $C_{ss}$ FOR MOST DRUGS

PHARMACOKINETIC MODELS

WHAT PHARMACOKINETIC PARAMETERS ARE PRIMARY?
**SINGLE COMPARTMENT MODEL**

\[ \text{DOSE} \rightarrow V_d \rightarrow \text{CL}_E \]

**ELIMINATION HALF-LIFE**

\[ t_{1/2} = \frac{0.693 \cdot V}{\text{CL}_E} \text{d(area)} \]

THEREFORE, \( t_{1/2} \) IS NOT A PRIMARY PHARMACOKINETIC PARAMETER

**3 DISTRIBUTION VOLUMES**

\[
\begin{align*}
V_{d \text{ (extrap.)}} &= \frac{\text{DOSE}}{C_0} \\
V_{d \text{ (area)}} &= \frac{t_{1/2} \cdot \text{CL}_E}{0.693} \\
V_{d \text{ (ss)}} &= V_1 + V_2 + \ldots + V_n
\end{align*}
\]
SOME DRUGS NOT ELIMINATED BY FIRST ORDER KINETICS

**PHENYTOIN (DILANTIN)**

**ETHYL ALCOHOL**

**ACETYLSALICYLIC ACID (ASPIRIN)**

---

PHENYTOIN HYDROXYLATION

[Chemical structure showing hydroxylation process]

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Graphs showing plasma concentrations, DPH elimination, urine creatinine, and DPH dose over time.
PHENYTOIN KINETICS in Normal Subjects

 STEADY STATE EQUATIONS

FIRST ORDER KINETICS

DOSE /τ = CL_e • C_{SS}

MICHAELIS - MENTEN KINETICS

DOSE /τ = \left[ \frac{V_{max}}{K_m + C_{SS}} \right] C_{SS}

RELATIONSHIP OF PLASMA LEVEL TO PHENYTOIN DOSE*

<table>
<thead>
<tr>
<th>PHENYTOIN DOSE (mg/day)</th>
<th>PLASMA LEVEL µg/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>300</td>
<td>10</td>
</tr>
<tr>
<td>400</td>
<td>20</td>
</tr>
<tr>
<td>500</td>
<td>30</td>
</tr>
</tbody>
</table>

(THERAPEUTIC RANGE: 10 – 20 µg/mL)

PATIENT WHO BECAME TOXIC ON A PHENYTOIN DOSE OF 300 mg/day

PHENYTOIN CASE HISTORY

After inpatient evaluation for a generalized seizure, a 28-year-old woman was discharged on phenytoin therapy at a dose of 300 mg/day.

After 5 days of therapy, she presented to the hospital’s emergency department with marked ataxia. Her phenytoin plasma concentration was found to be 27 μg/mL. She was sent home on a reduced phenytoin dose of 200 mg/day.

PHENYTOIN CASE HISTORY (cont.)

Two days later, she returned to the emergency department with more severe ataxia. Her phenytoin plasma concentration was now 32 μg/mL. Non-compliance was suspected but a clinical pharmacology evaluation was requested.
PATIENT with VERY LOW $V_{\text{MAX}}$

$V_{\text{MAX}} = 132 \text{ mg/day}$

DOSE mg/day

PHENYTIN $\mu g/mL$

BASIS OF APPARENT FIRST-ORDER KINETICS

\[
\frac{dC}{dt} = \frac{V_{\text{max}}}{K_m + C} C
\]

If $K_m > C$:

\[
\frac{dC}{dt} = \frac{V_{\text{max}}}{K_m} C = "k" C
\]

CONCLUDING THOUGHTS

- PRACTICE PROBLEMS AT END OF CHAPTER 2 WITH ANSWERS IN APPENDIX II
- EQUATIONS DERIVED IN “PRINCIPLES OF CLINICAL PHARMACOLOGY” TEXTBOOK
- LAPLACE TRANSFORMS INTRODUCED WITH TABLES IN APPENDIX I