CLINICAL PHARMACOKINETICS

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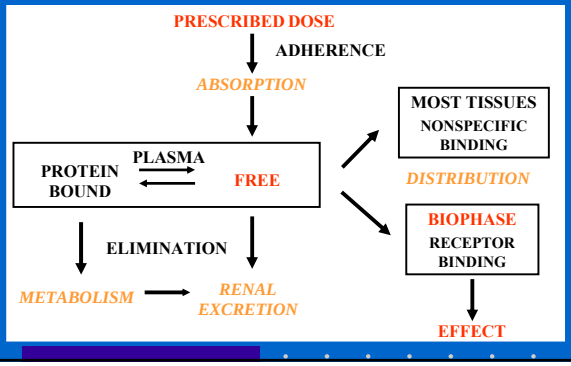
USES OF PHARMACOKINETICS

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

TARGET CONCENTRATION STRATEGY

ESTIMATE INITIAL DOSE
TARGET LEVEL
LOADING DOSE
MAINTENANCE DOSE
⇩
BEGIN THERAPY
⇩
ASSESS THERAPY
PATIENT RESPONSE
DRUG LEVEL
⇩
REFINE DOSE ESTIMATE
⇩
ADJUST DOSE

RATIONALE FOR PLASMA LEVEL MONITORING



FIRST DESCRIPTION OF THERAPEUTIC DRUG MONITORING

Wuth O. JAMA 1927;88:2013-17.

RADIOIMMUNOASSAY

Rosalyn Sussman Yalow -1977 Nobel Laureate

GAS LIQUID CHROMATOGRAPHY

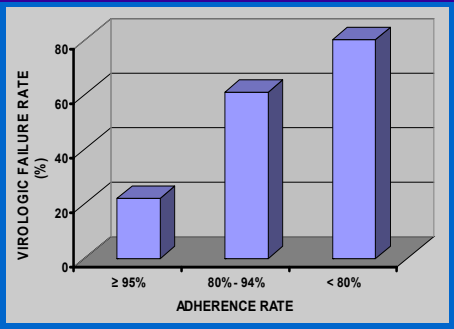
HIGH PERFORMANCE LIQUID CHROMATOGRAPHY

FLUORESCENCE POLARIZATION IMMUNOASSAY

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



From: Paterson DL, et al. Ann Intern Med 2000;133:21-30.

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

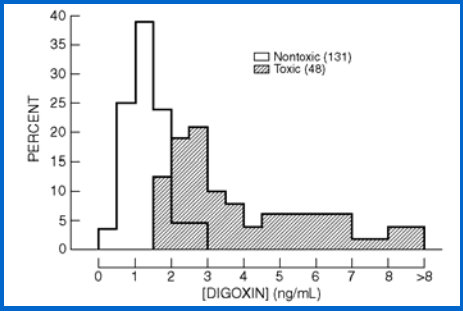
ESTIMATE INITIAL DOSE

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"*

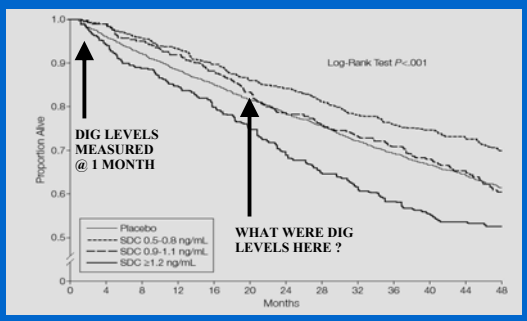
↑ Risk of toxicity in patients with coronary heart disease, hypoxemia, and/or hypokalemia, hypomagnesemia

↓ 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

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



* Rathore SS, et al. JAMA 2003;289:871-8.

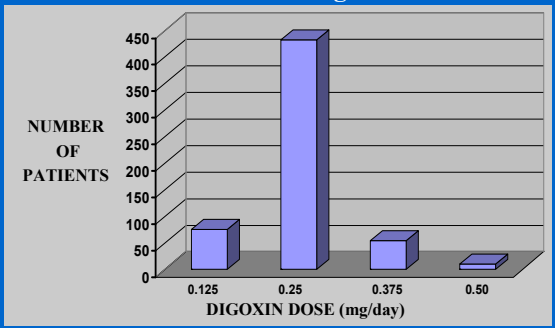
PROPOSED Range of DIGOXIN LEVELS for *OPTIMAL THERAPY* in CHF

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



Rathore SS, et al. JAMA 2003, 289:871-8.

TARGET CONCENTRATION STRATEGY

ESTIMATE INITIAL DOSE

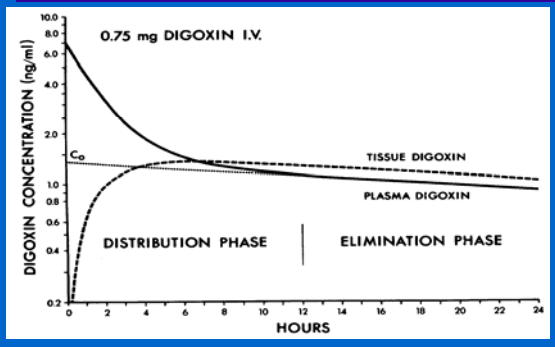
TARGET LEVEL

LOADING DOSE

MAINTENANCE DOSE

BASED ON CONCEPT OF DISTRIBUTION VOLUME

DIGOXIN LEVELS after IV Dose



INITIAL *DIGITALIZATION*

DIGITALIZING DOSE
0.75 mg = 750 x 10^3 ng

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

1.4 ng/mL

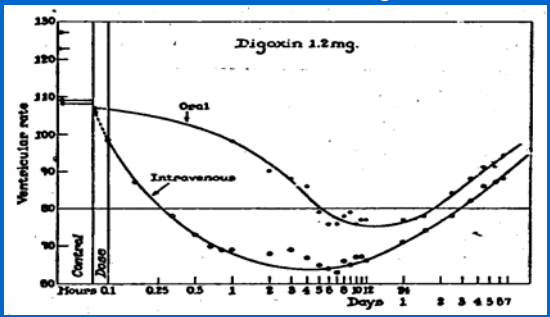
3 DISTRIBUTION VOLUMES

$$V_{d\,(extrap.)} = DOSE \,/\, C_0$$

$$V_{d\,(area)} = \frac{t_{1/2} \bullet CL_E}{0.693}$$

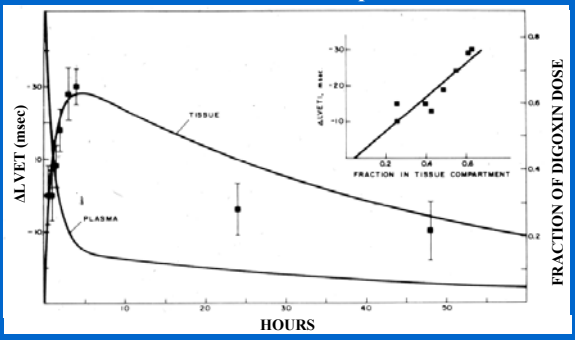
$$V_{d\,(ss)} = V_1 + V_2 + \ldots\ldots V_n$$

DISTRIBUTION DELAYS ONSET of DIGOXIN Chronotropic Action*



* From Gold H, et al. J Pharmacol Exp Ther 1953;109:45-57.

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

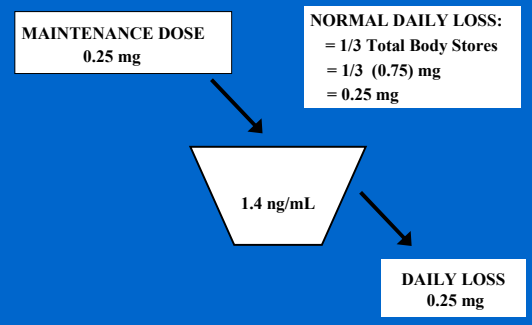
$$t_{1/2} = \frac{0.693 \ V_d}{CL_E}$$

$$k = \frac{0.693}{t_{1/2}}$$

$$CL_E = k \times V_d$$

$t_{1/2}$ = elimination half life
k = elimination rate constant
CL_E = elimination clearance

MAINTENANCE DIGOXIN THERAPY



DIGOXIN CUMULATION

.25 x 2/3 = .17 DOSE #1
+.25 DOSE #2
.42 x 2/3 = .28
+.25 DOSE #3
.53 x 2/3 = .36
+.25 DOSE #4
.61 x 2/3 = .41
+.25 DOSE #5
.66 x 2/3 = .44
+.25 DOSE #6
.69 x 2/3 = .46
+.25 DOSE #7
.71

CUMULATION FACTOR

$$CF = \frac{1}{\left(1 - e^{-k\tau}\right)}$$

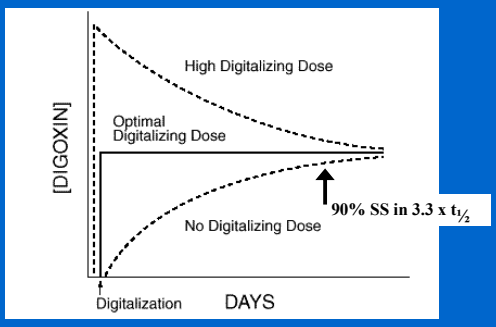
τ = dose interval

k = elimination rate constant

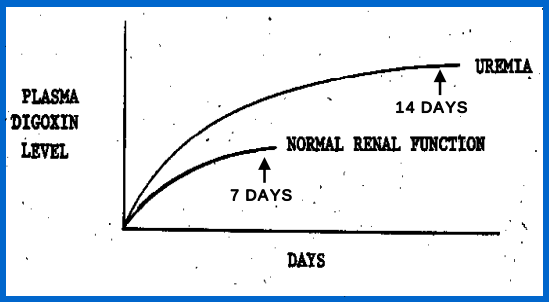
ELIMINATION RATE CONSTANT

$$k = \frac{0.693}{t_{1/2}}$$

LOADING & MAINTENANCE DOSES



TIME-COURSE OF DIGOXIN CUMULATION



DIGOXIN CASE HISTORY

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.

DIGOXIN CASE HISTORY (cont.)

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.

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PATIENT RESPONSE
DRUG LEVEL
⇩
REFINE DOSE ESTIMATE
⇩
ADJUST DOSE

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PHARMACOKINETIC ANALYSIS OF DIGOXIN CASE HISTORY

ESTIMATED $T_{1/2}$:
4.3 days (k = 0.16 day^{-1})
***TIME TO 90% STEADY STATE*:**
3.3 x 4.3 = 14.2 days
***STEADY STATE PEAK LEVEL*:**
6.2 ng/mL (post distribution phase)
***MEASURED LEVEL*:**
6.9 ng/mL (pre distribution)

STEADY STATE CONCENTRATION

CONTINUOUS INFUSION:

$$C_{SS} = \frac{I}{CL_E}$$

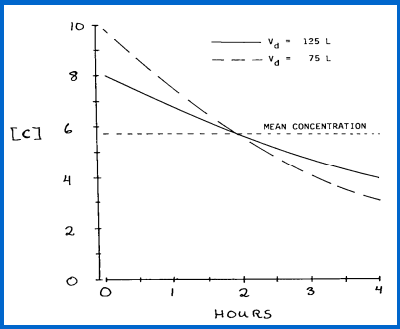
INTERMITTENT DOSING:

$$\overline{C}_{SS} = \frac{DOSE/\tau}{CL_E}$$

STEADY STATE CONCENTRATION

- ***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



FOR MOST DRUGS, C_{ss} IS PROPORTIONAL TO DOSE (Dosing Rate)

CONTINUOUS INFUSION:

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

INTERMITTENT DOSING:

$$\overline{C}_{ss} = \frac{DOSE/\tau}{CL_E}$$

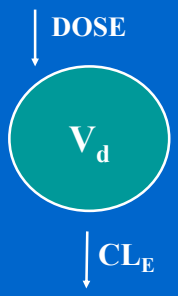
STEADY STATE CONCENTRATION

- ***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



ELIMINATION HALF-LIFE

$$t_{1/2} = \frac{0.693 \bullet V_{d\,(area)}}{CL_E}$$

THEREFORE, $t_{1/2}$ IS *NOT* A PRIMARY PHARMACOKINETIC PARAMETER

3 DISTRIBUTION VOLUMES

$$V_{d\,(extrap.)} = DOSE \,/\, C_0$$

$$V_{d\,(area)} = \frac{t_{1/2} \bullet CL_E}{0.693}$$

$$V_{d\,(ss)} = V_1 + V_2 + \ldots\ldots V_n$$

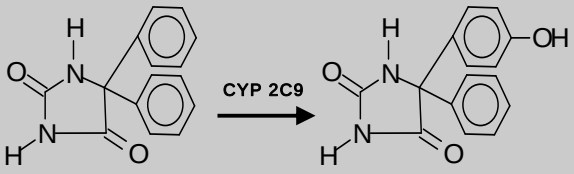
SOME DRUGS *NOT* ELIMINATED BY FIRST ORDER KINETICS

PHENYTOIN **(DILANTIN)**

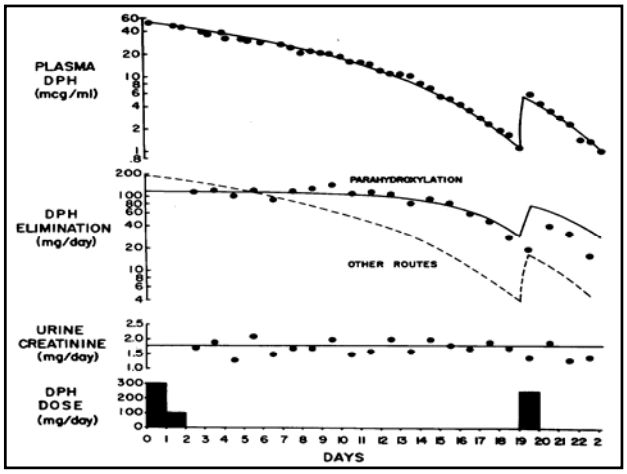
ETHYL ALCOHOL

ACETYLSALICYLIC ACID **(ASPIRIN)**

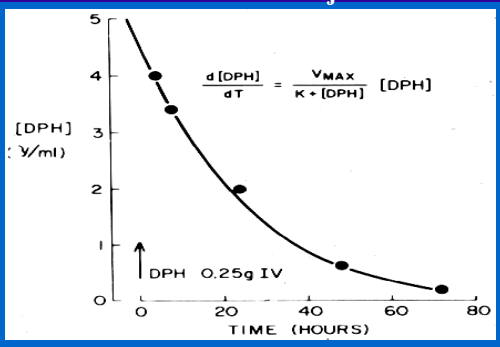
PHENYTOIN HYDROXYLATION



PHENYTOIN ***p*** **- HPPH**



PHENYTOIN KINETICS in Normal Subjects



STEADY STATE EQUATIONS

FIRST ORDER KINETICS

$$\text{DOSE}/\tau = CL_E \bullet \overline{C}_{SS}$$

MICHAELIS - MENTEN KINETICS

$$\text{DOSE}/\tau = \left[\frac{V_{max}}{K_m + \overline{C}_{SS}}\right] \overline{C}_{SS}$$

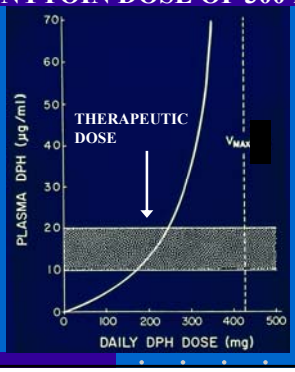
RELATIONSHIP OF PLASMA LEVEL TO PHENYTOIN DOSE*

PHENYTOIN DOSE (mg/day)	PLASMA LEVEL µg/mL
300	10
400	20
500	30

(THERAPEUTIC RANGE: 10 – 20 µg/mL)

* From: Kutt H, McDowell F: J Am Med Assoc 1968;203:969-72.

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



PHENYTOIN CASE HISTORY

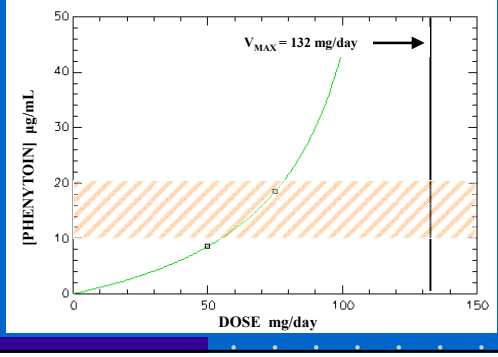
After inpatient evaluation for a generalized seizure, a 28-year-old woman was discharged on *phenytoin* therapy at a dose of 300 mg/day.

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_{MAX}



BASIS OF *APPARENT* FIRST-ORDER KINETICS

$$\frac{dC}{dt} = \left[\frac{V_{max}}{K_m + C} \right] C$$

If $K_m > C$:

$$\frac{dC}{dt} = \left[\frac{V_{max}}{K_m} \right] C = "k" C$$

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