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

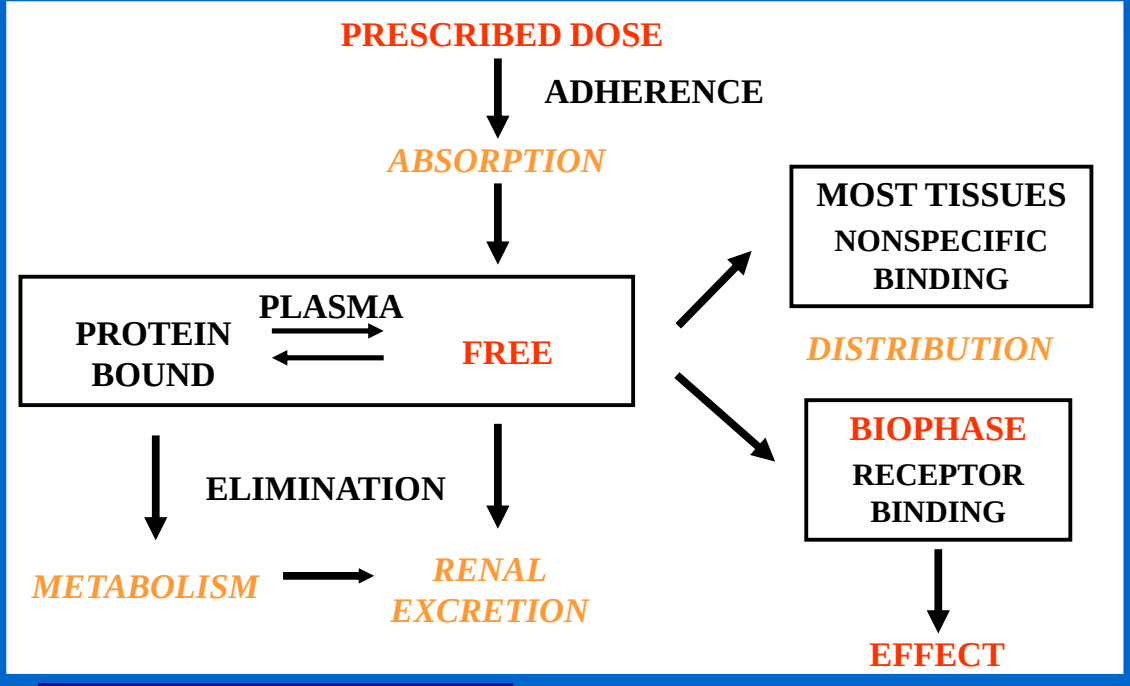
⇩

REFINE DOSE ESTIMATE

⇩

ADJUST DOSE

RATIONALE FOR PLASMA LEVEL MONITORING



FIRST DESCRIPTION OF THERAPEUTIC DRUG MONITORING

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

BROMIDE TREATMENT—WUTH

RATIONAL BROMIDE TREATMENT

OTTO WUTH, M.D.

RADIOIMMUNOASSAY

Rosalyn Sussman Yalow -1977 Nobel Laureate

First Academic Clinical Drug Analysis Lab

Arthur J. Atkinson, Jr., M.D.
Northwestern Memorial Hospital
Chicago, Illinois

GAS LIQUID CHROMATOGRAPHY

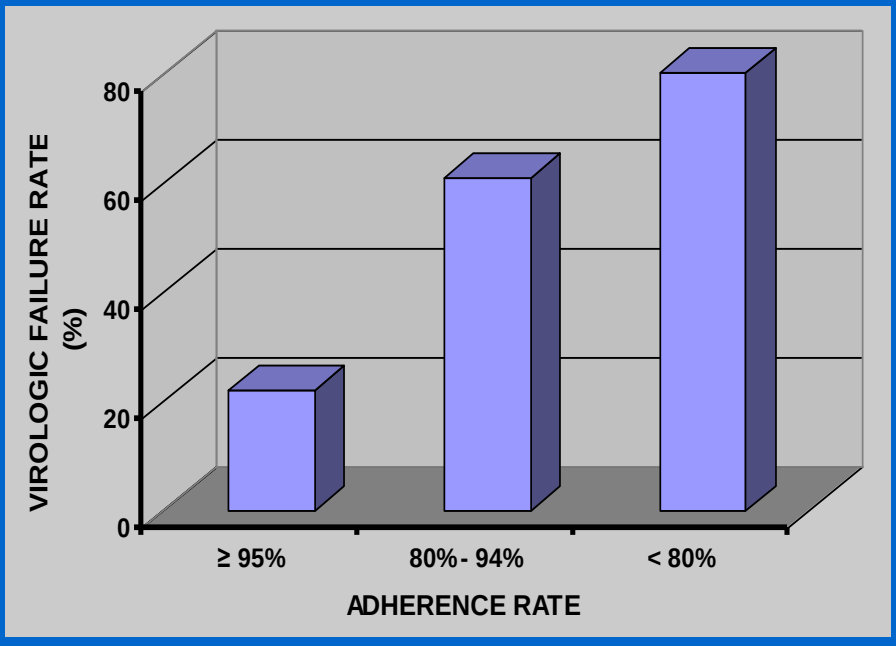
HIGH PERFORMANCE LIQUID CHROMATOGRAPHY

FLUORESCENCE POLARIZATION IMMUNOASSAY

DRUG CANDIDATES FOR TDM

- Low therapeutic index
- No physiologic endpoints or biomarkers 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

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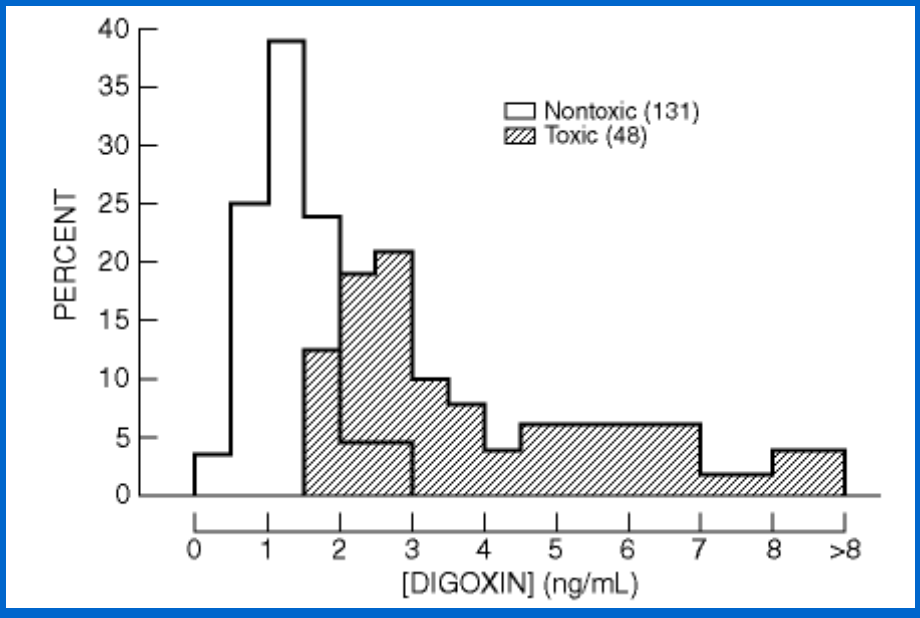
MAINTENANCE DOSE

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"*

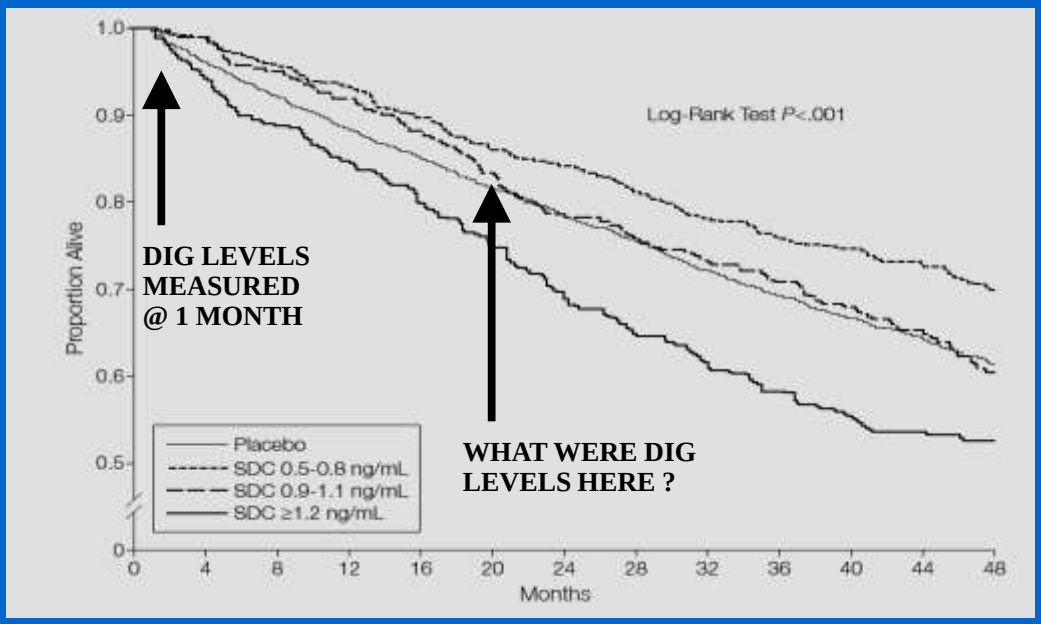
↑ **Risk of toxicity in patients with coronary heart disease, hypoxemia, and/or hypokalemia, hypomagnesemia**

↓ **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.

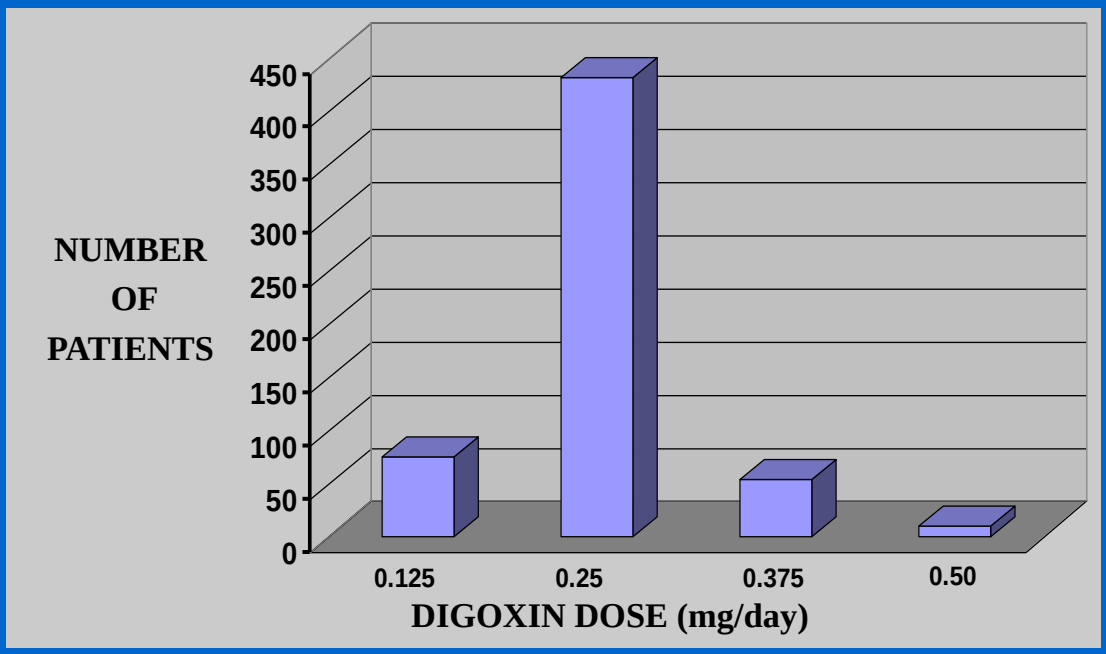
PROPOSED Range of DIGOXIN LEVELS for *OPTIMAL THERAPY* in CHF

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

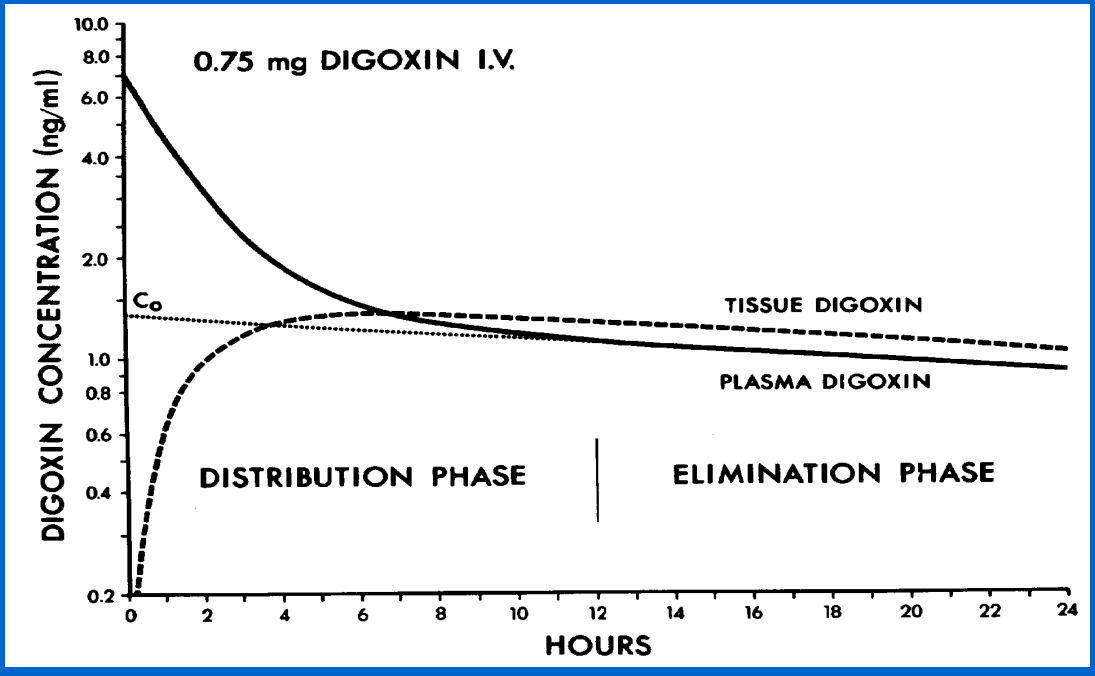
TARGET LEVEL

LOADING DOSE

MAINTENANCE DOSE

BASED ON CONCEPT OF DISTRIBUTION VOLUME

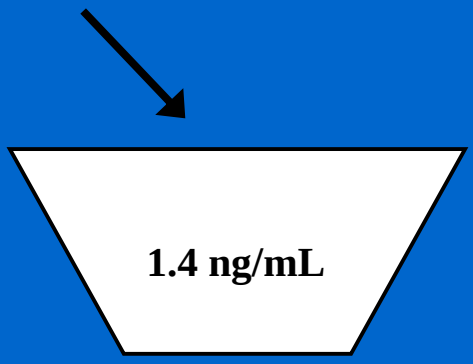
DIGOXIN LEVELS after IV Dose



INITIAL *DIGITALIZATION*

DIGITALIZING DOSE
0.75 mg = 750 x 10^3 ng

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



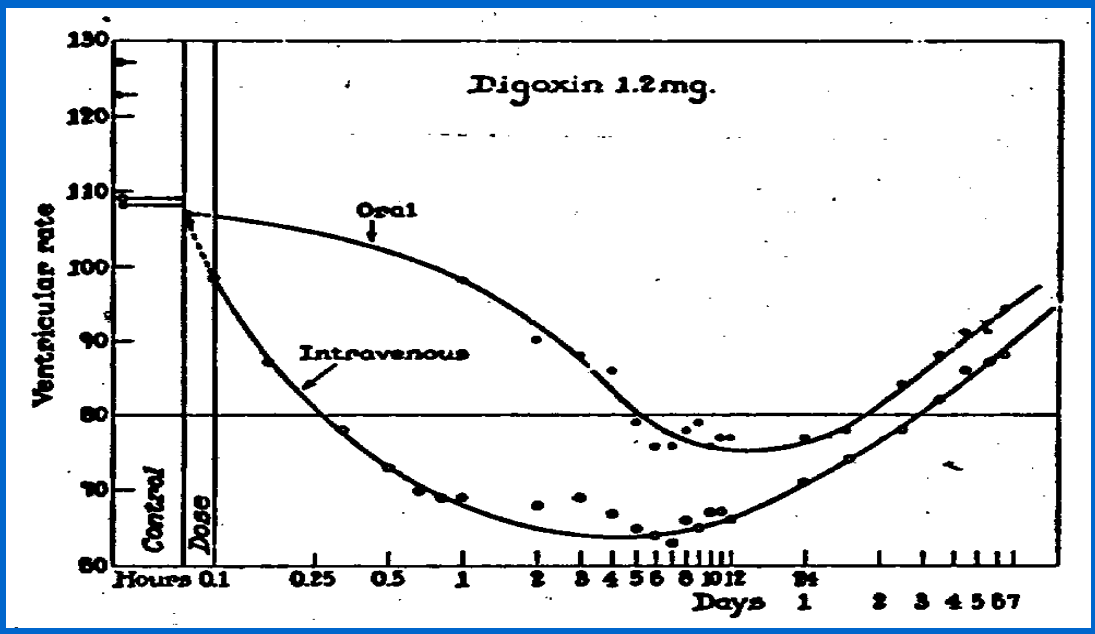
3 DISTRIBUTION VOLUMES

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

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

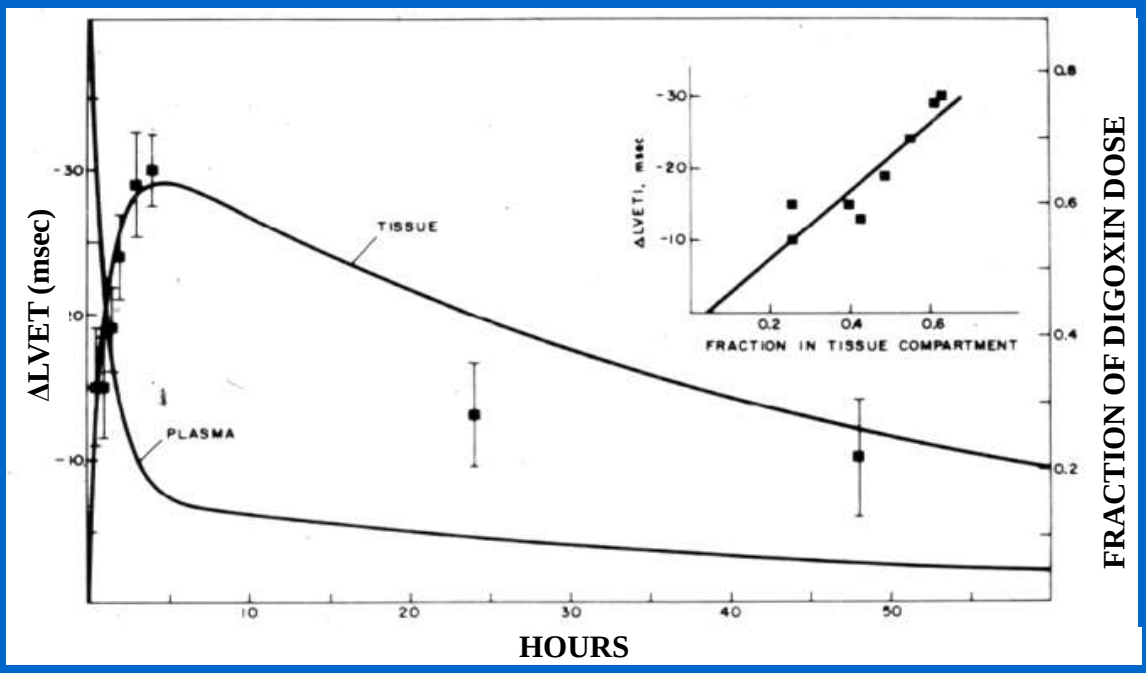
$$V_{d\,(ss)} = V_1 + V_2 + \ldots\ldots V_n$$

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

MAINTENANCE DOSE
0.25 mg

NORMAL DAILY LOSS:
= 1/3 Total Body Stores
= 1/3 (0.75) mg
= 0.25 mg

DAILY LOSS
0.25 mg

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

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

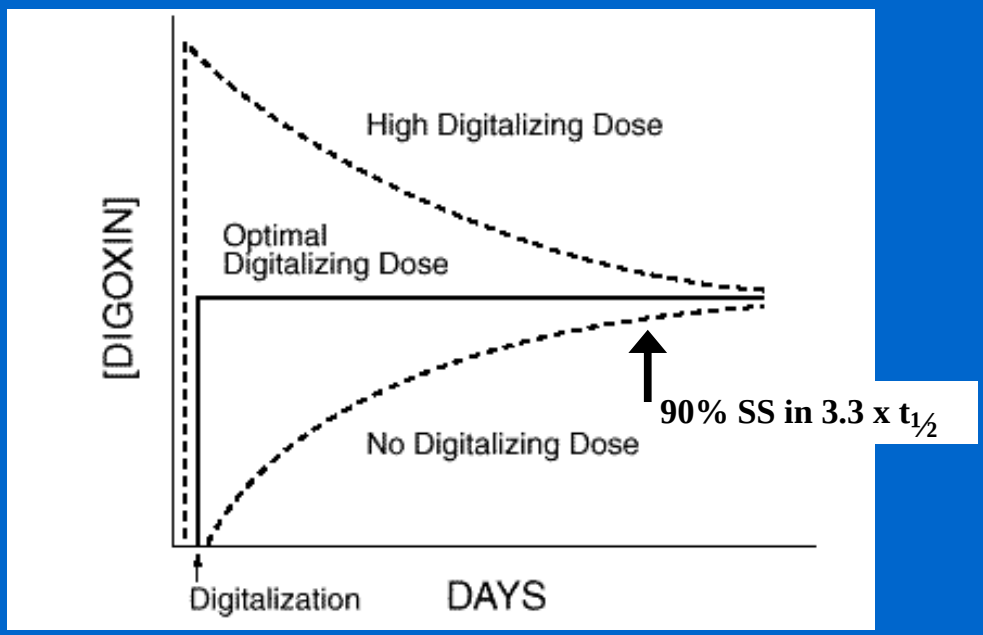
τ = dose interval

k = elimination rate constant

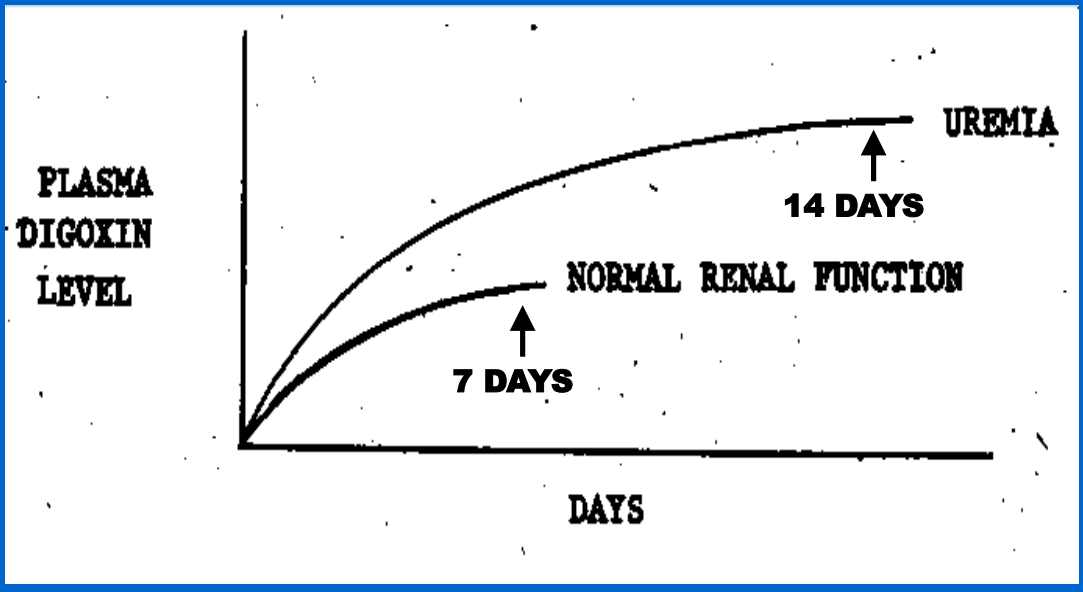
ELIMINATION RATE CONSTANT

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

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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⇩

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PATIENT RESPONSE

DRUG LEVEL

⇩

REFINE DOSE ESTIMATE

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ADJUST DOSE

TARGET CONCENTRATION STRATEGY

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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:

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

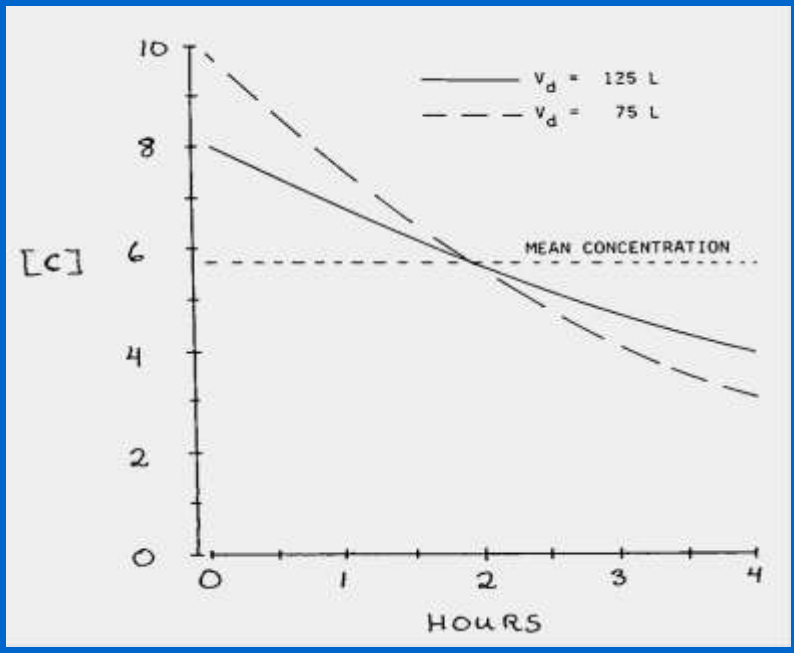
INTERMITTENT DOSING:

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

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:

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

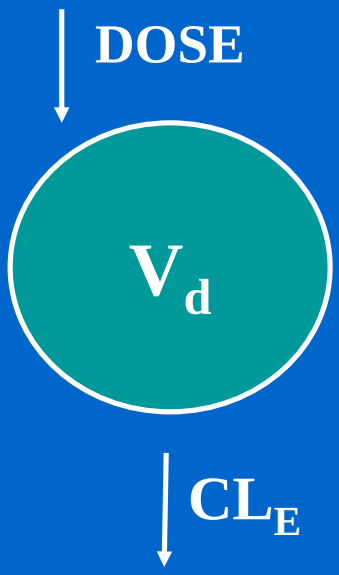
STEADY STATE CONCENTRATION

- ***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*

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

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

$$V_{d(ss)} = V_1 + V_2 + ... V_n$$

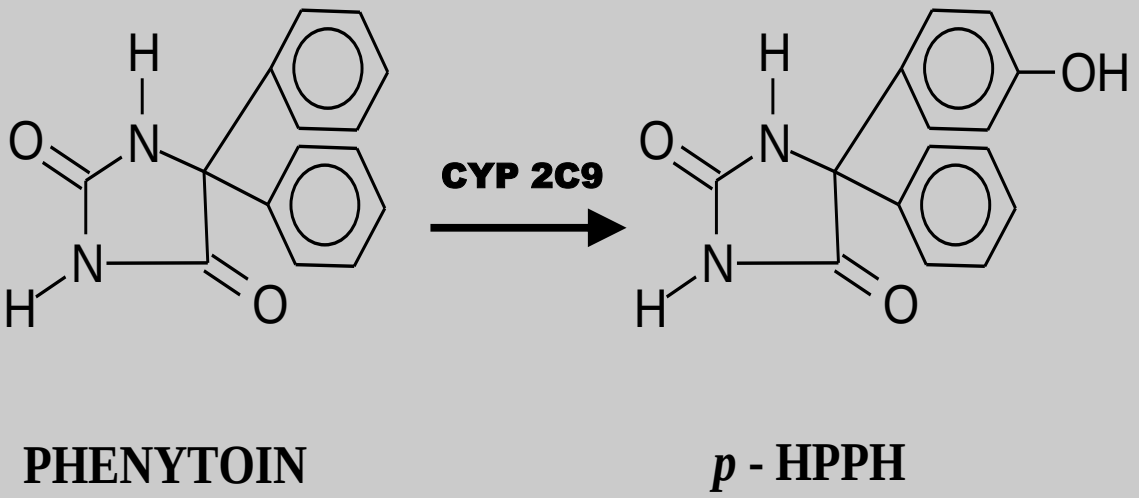
SOME DRUGS *NOT* ELIMINATED BY FIRST ORDER KINETICS

PHENYTOIN **(DILANTIN)**

ETHYL ALCOHOL

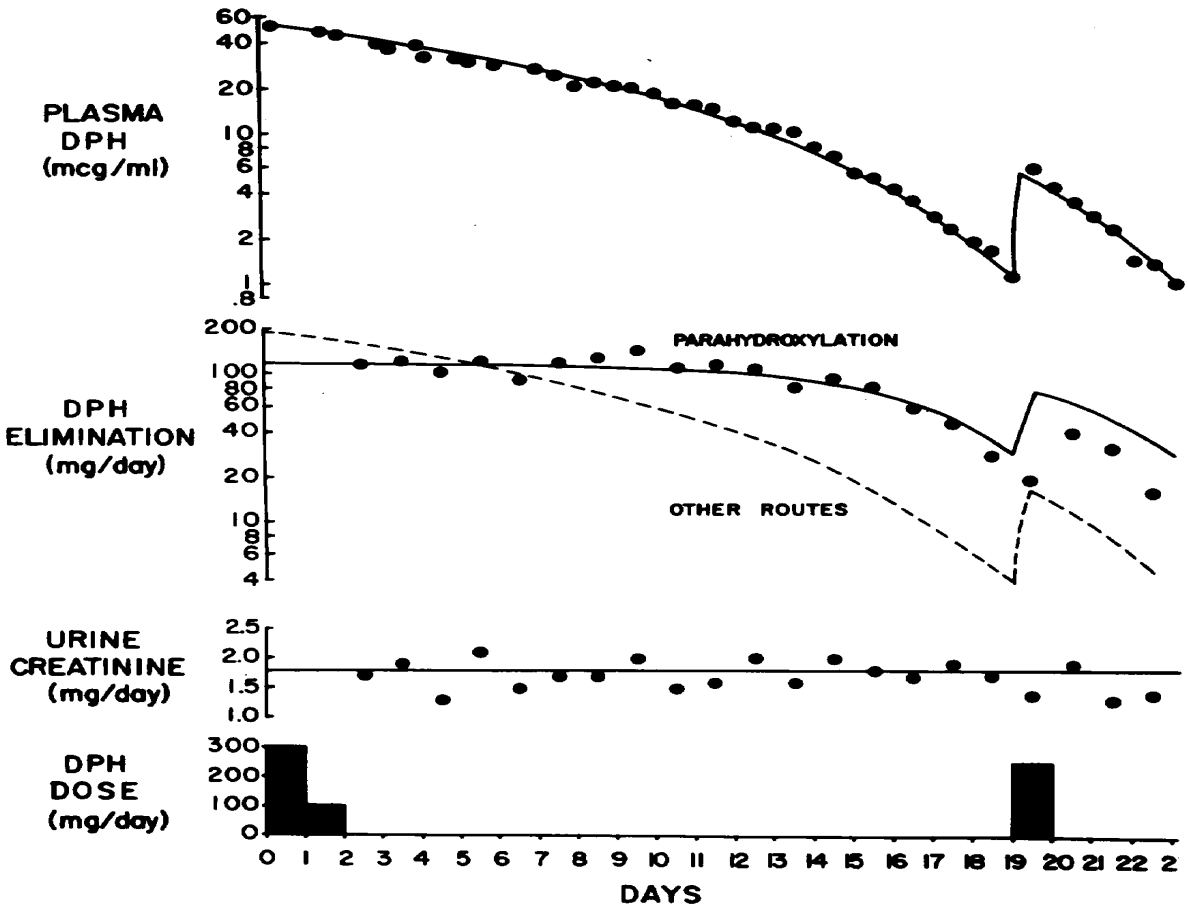
ACETYLSALICYLIC ACID **(ASPIRIN)**

PHENYTOIN HYDROXYLATION

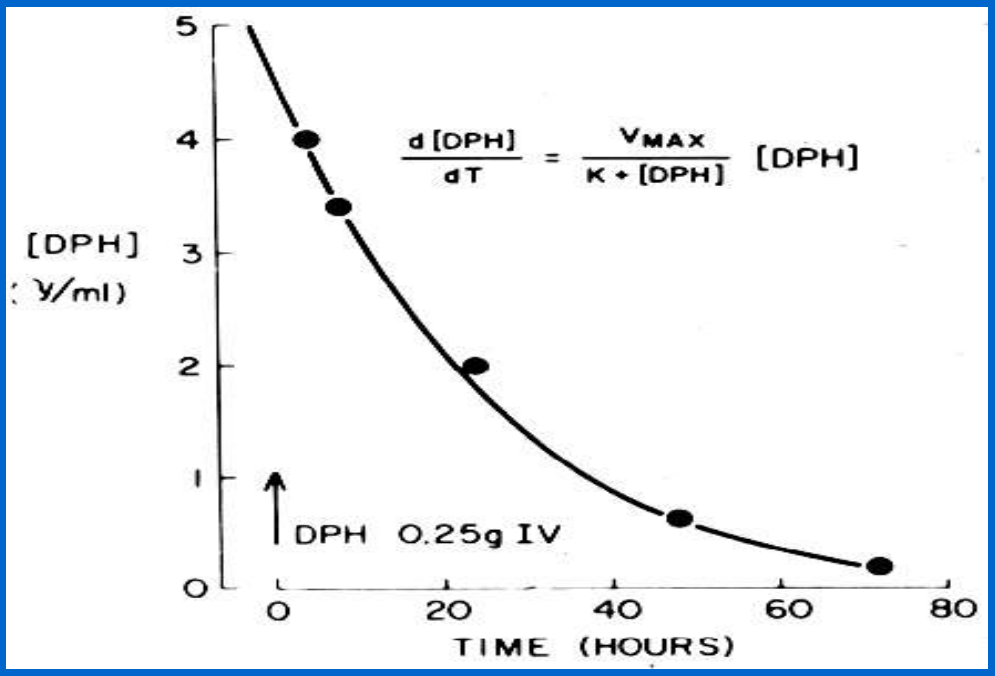


PHENYTOIN

p - HPPH


PLASMA DPH (mcg/ml)
60
40
20
10
8
6
4
2
1
.8
DPH ELIMINATION (mg/day)
200
100
80
60
40
20
10
8
6
4
PARAHYDROXYLATION
OTHER ROUTES
URINE CREATININE (mg/day)
2.5
2.0
1.5
1.0
DPH DOSE (mg/day)
300
200
100
0
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 2
DAYS

PHENYTOIN KINETICS
in Normal Subjects



STEADY STATE EQUATIONS

FIRST ORDER KINETICS

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

MICHAELIS - MENTEN KINETICS

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

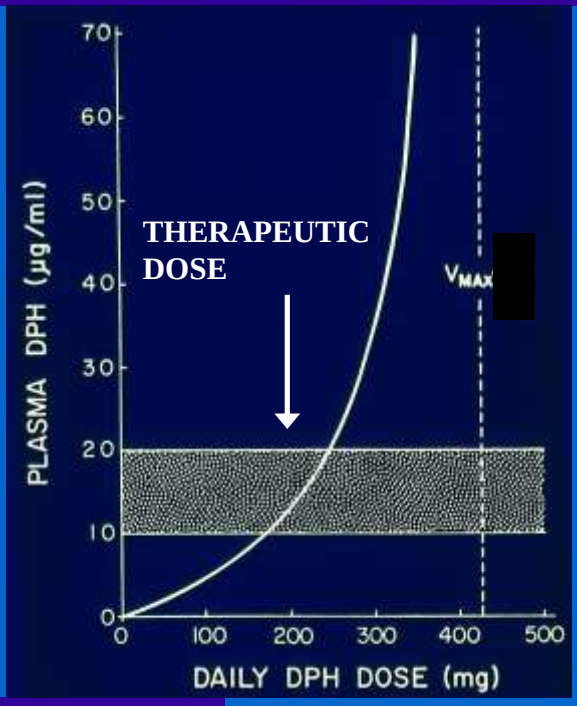
RELATIONSHIP OF PLASMA LEVEL TO PHENYTOIN DOSE*

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

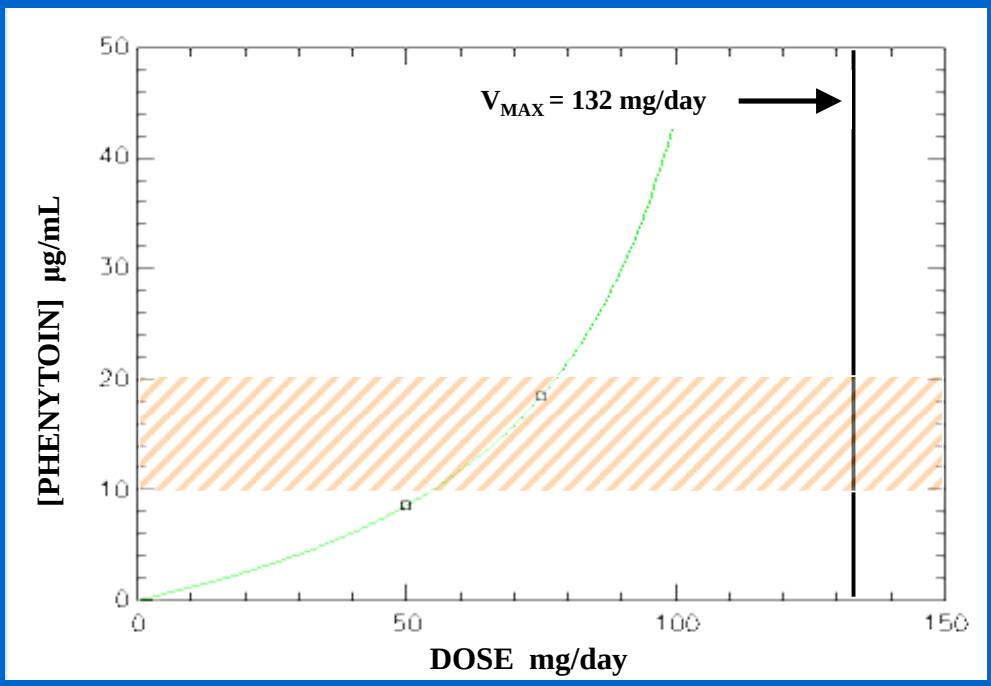
After inpatient evaluation for a generalized seizure, a 28-year-old woman was discharged on *phenytoin* therapy at a dose of 300 mg/day.

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 $K_m > C$:

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

PHARMACOKINETICS

- *PRACTICE PROBLEMS* AT END OF CHAPTER 2 WITH *ANSWERS* IN APPENDIX II
- *EQUATIONS* DERIVED IN "PRINCIPLES OF CLINICAL PHARMACOLOGY" TEXTBOOK