



CLINICAL PHARMACOKINETICS

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Education**

National Institutes of Health

Clinical Center

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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



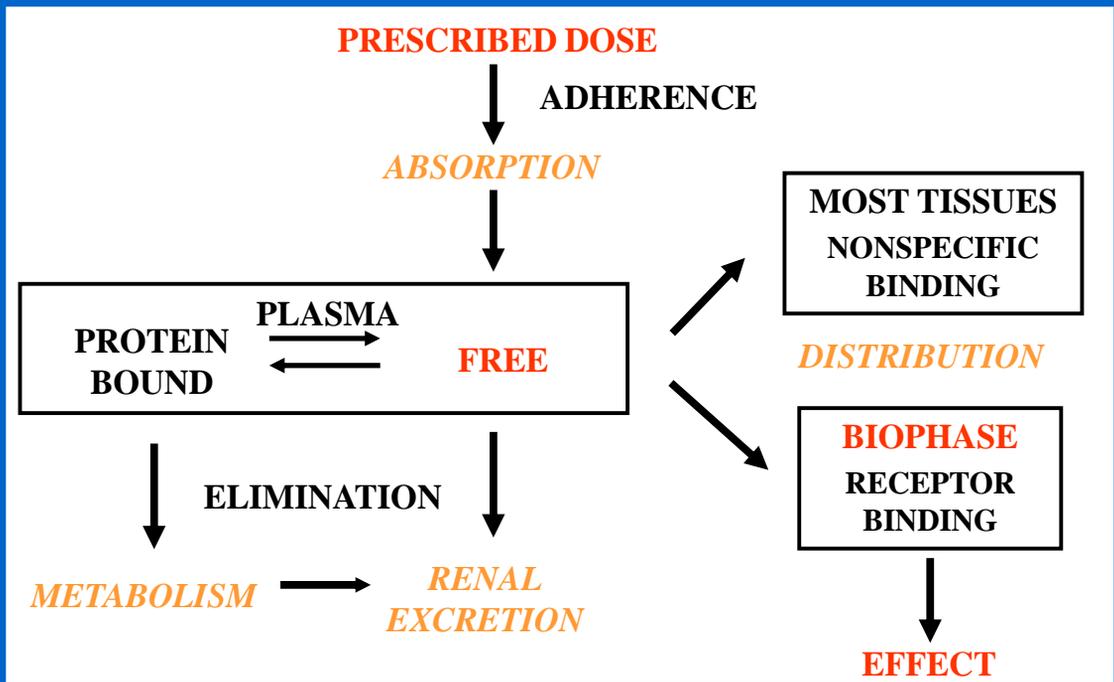
REFINE DOSE ESTIMATE



ADJUST DOSE



RATIONALE FOR PLASMA LEVEL MONITORING



FIRST DESCRIPTION OF THERAPEUTIC DRUG MONITORING

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

BROMIDE TREATMENT—MUTH

covered. On the whole, then, in the present state of our knowledge, perhaps the most general assumption is that spasmolytic (muscle) and generally a more hypotensive effect as it has been shown to do in some of the most peculiar, severe contractions and blood vessels in man. In this case it would serve under ordinary conditions, if present in all its spasmolytic, sedative, or distal action, another normal function of the blood. Under other conditions its stimulating effect would come into play. The question remains as to how strongly it affects. But it is an active constituent, perhaps, than a simple sedative in which all have become reconciled; namely, that persistent stimulation of a steady nerve may result in either full or one of several purposes, depending on various circumstances, including but especially on the amount of stimulus applied. Indeed, this conception of the action of spasmolytics will be recognized as conforming generally to Vavassori's theory that inhibition, in general, is due to subnormal stimulation.

NATIONAL BROMIDE TREATMENT
NEW ADDRESS AND ITS CONTENTS.*

OTTO WUTH, M.D.
Assistant Professor, Johns Hopkins University, Baltimore, Md.

Bromide treatment to be reduced most, on the one hand, produce the desired effect of the drug and, on the other hand, avoid the danger of bromide intoxication. The boundaries of bromide action, and consequently also those of a rational treatment, are laid on the relations between bromides and bromide—the chloro-bromide equilibrium or replacement-which themselves have to be discussed briefly.

Indeed, chloride constitutes the greater part of the character of the body, and its ions are essential for the function of many cells. Hence it is naturally retained, outside of the urine, it may be necessarily excreted. The body contains an almost constant amount of chloride ion. The excretion varies with the salt intake but has a maximum limited to some 400 mgm. in 24 hours (Elliott and Elliott), which is nearly constant, and therefore is reached within three or four days. If the supply of salt is stopped, excretion falls within three days to a lower level, but the body retains its normal salt content.

The retention of chloride can be hastened by the administration of bromides and iodides. Conversely, the administration of chloride hastens the elimination of these salts.

If bromide and chloride enter the body their excretion starts rapidly but proceeds very slowly; as usually, in fact, that even twenty days after treatment has been stopped the excretion of bromide is not completed. Hence a retention of bromide when given?

*From *Laboratory of Physical Chemistry, Johns Hopkins University, Baltimore, Md.*
 1. *Ann. N. Y. Acad. Sci.*, 1926, 27, 1-18.
 2. *Ann. N. Y. Acad. Sci.*, 1926, 27, 1-18.
 3. *Ann. N. Y. Acad. Sci.*, 1926, 27, 1-18.
 4. *Ann. N. Y. Acad. Sci.*, 1926, 27, 1-18.
 5. *Ann. N. Y. Acad. Sci.*, 1926, 27, 1-18.
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 8. *Ann. N. Y. Acad. Sci.*, 1926, 27, 1-18.
 9. *Ann. N. Y. Acad. Sci.*, 1926, 27, 1-18.
 10. *Ann. N. Y. Acad. Sci.*, 1926, 27, 1-18.

which is due to the fact mentioned that bromide is given before chloride. Thus a sort of "bromide" condition of the body with bromide takes place, so that after a certain period in postoperative conditions no more bromide can be retained, and intake and excretion are balanced. The chloride content of the blood in this condition, the chloride having been partly replaced by bromide.

A calculation of more than 40 per cent of the chloride of the blood by bromide, according to Bromide's law. Inoperative symptoms generally appear, according to the experience of [1926] ground for substitution of the serum, when from about 25 to 30 per cent of the total halogens are represented by bromide; these rates, however, individual differences, a fact that must be borne in mind.

After this, it is easily understood that the action of the bromide medication depends not only on the law

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RADIOIMMUNOASSAY



Rosalyn Sussman Yalow -1977 Nobel Laureate

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First Academic Clinical Drug Analysis Lab

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

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GAS LIQUID CHROMATOGRAPHY



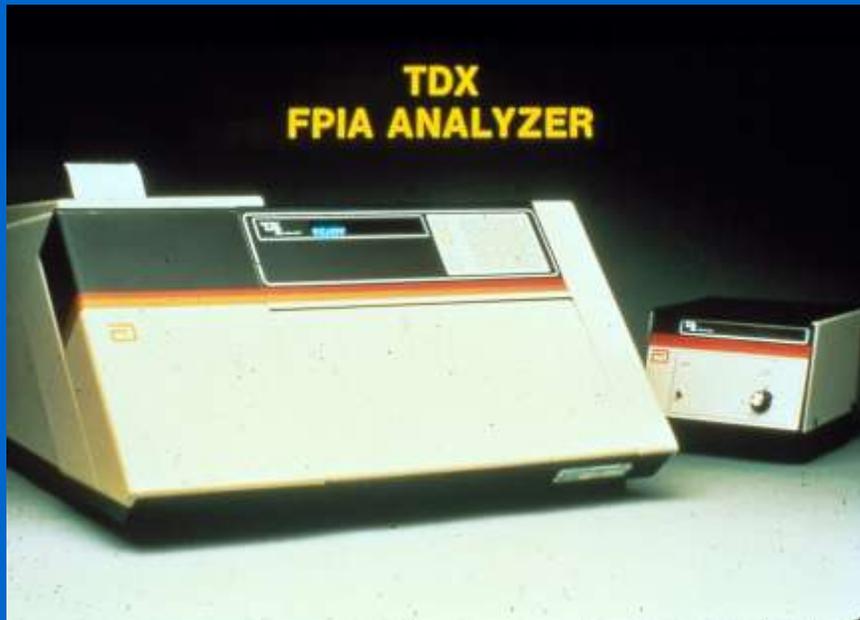
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HIGH PERFORMANCE LIQUID CHROMATOGRAPHY



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FLUORESCENCE POLARIZATION IMMUNOASSAY

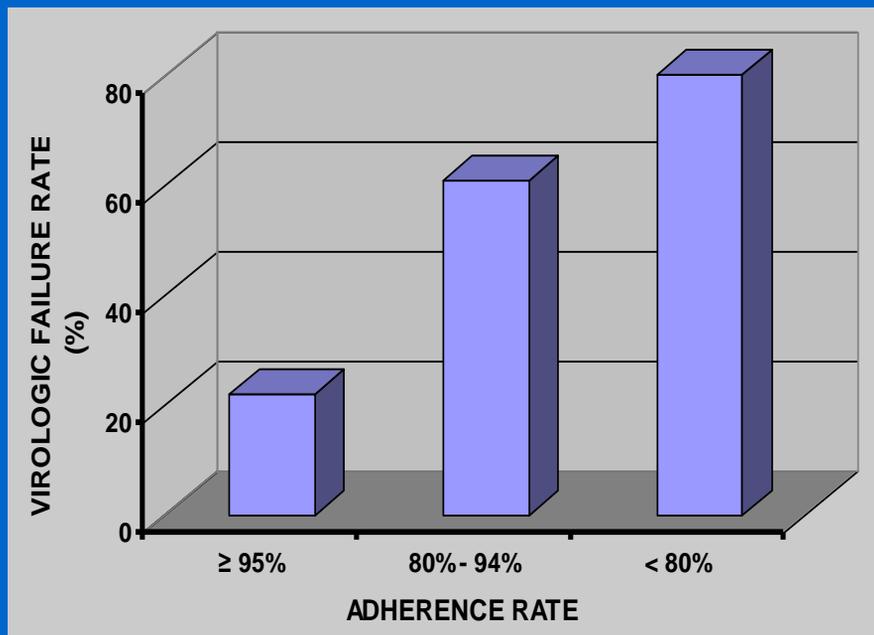




DRUG CANDIDATES FOR TDM

- **Low therapeutic index**
 - **No physiologic endpoints or biomarkers to guide dosage**
 - **Pharmacokinetics vary widely between individuals**
 - **Need to monitor adherence?**
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EFFECT OF *ADHERENCE* RATE ON OUTCOME IN HIV INFECTED PATIENTS



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

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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*
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TARGET CONCENTRATION STRATEGY

ESTIMATE INITIAL DOSE

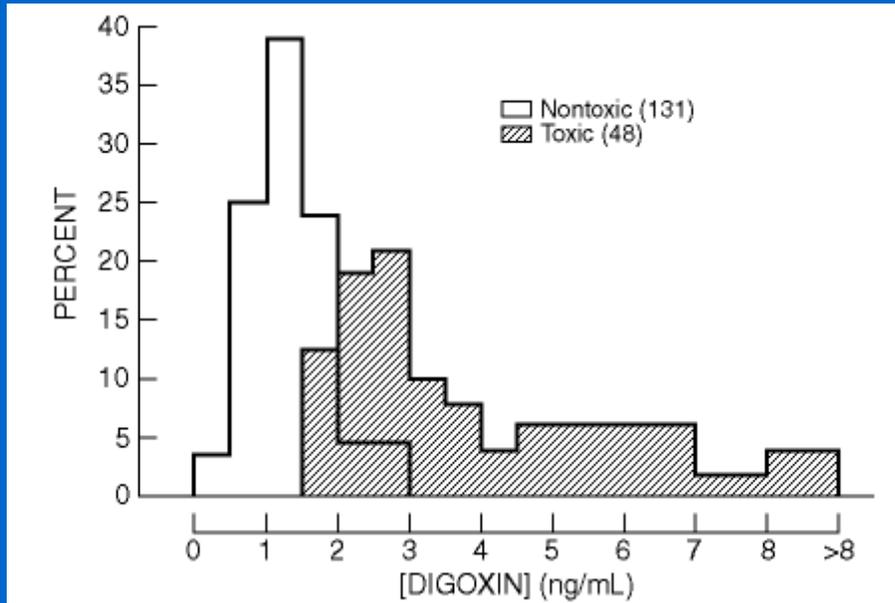
TARGET LEVEL

LOADING DOSE

MAINTENANCE DOSE

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DIGOXIN Levels in *TOXIC* and *NONTOXIC* Patients*



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

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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
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TRADITIONAL Guidelines for **DIGOXIN** Levels

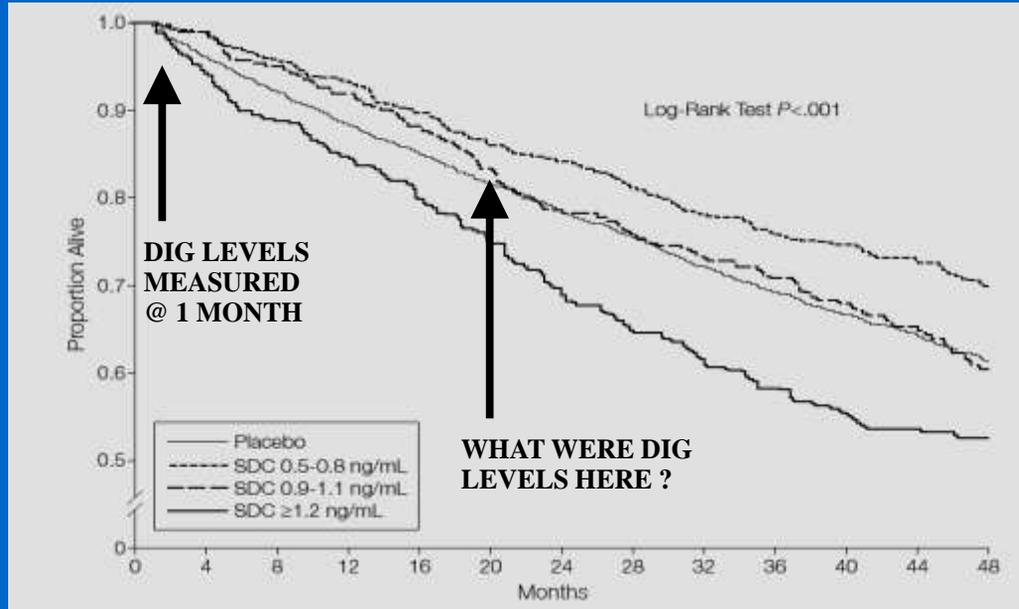
THERAPEUTIC RANGE: 0.8 - 1.6 ng/mL

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*



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

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

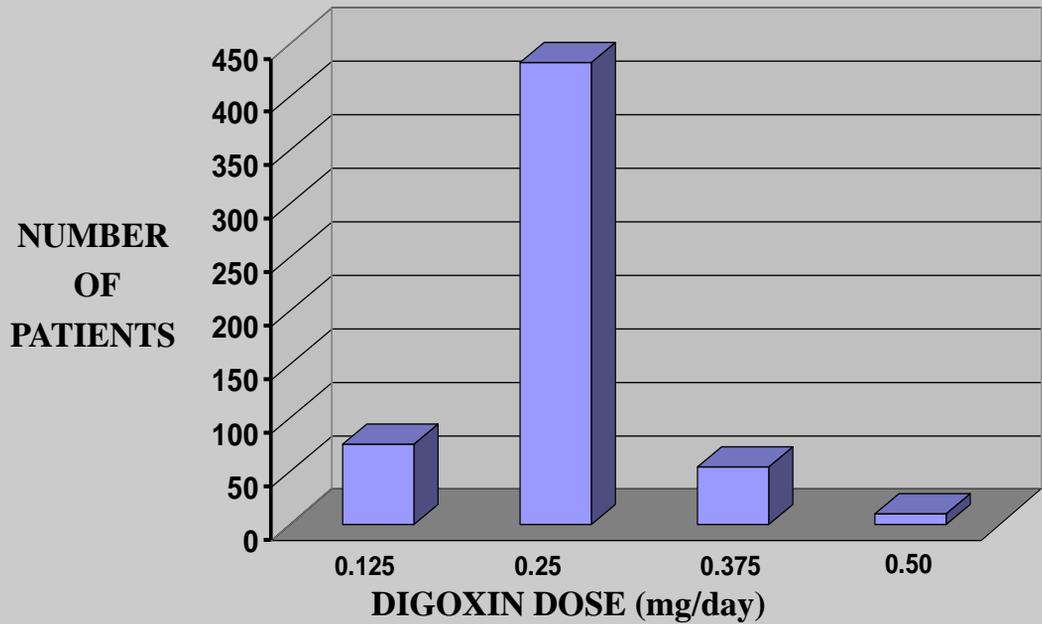
New Therapeutic Range: 0.5 - 0.9 ng/mL

**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?***

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DIGOXIN DOSES for Patients with Levels of 0.5 - 0.8 ng/mL



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

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TARGET CONCENTRATION STRATEGY

ESTIMATE INITIAL DOSE

TARGET LEVEL

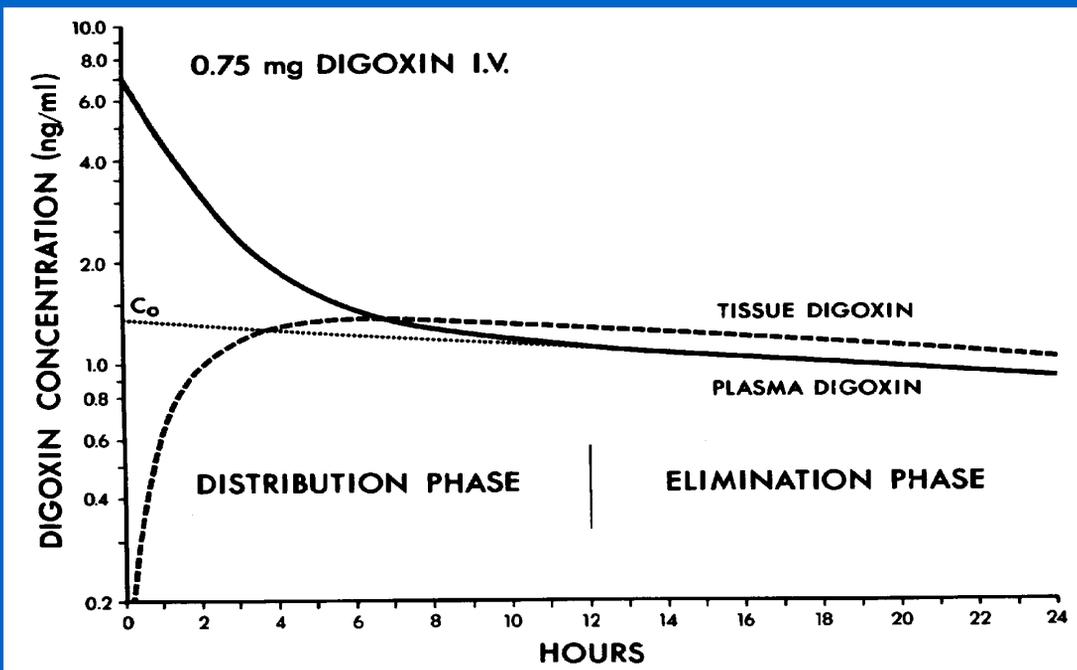
LOADING DOSE

MAINTENANCE DOSE

**BASED ON CONCEPT OF
DISTRIBUTION VOLUME**

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DIGOXIN LEVELS after IV Dose



INITIAL *DIGITALIZATION*

DIGITALIZING DOSE
 $0.75 \text{ mg} = 750 \times 10^3 \text{ ng}$

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

1.4 ng/mL

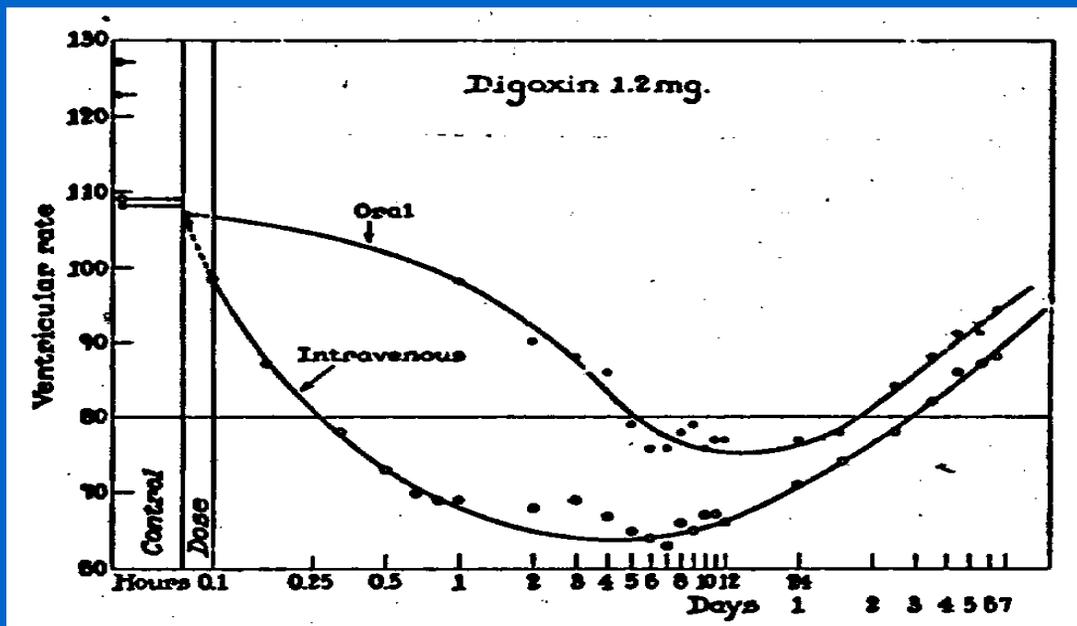
3 DISTRIBUTION VOLUMES

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

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

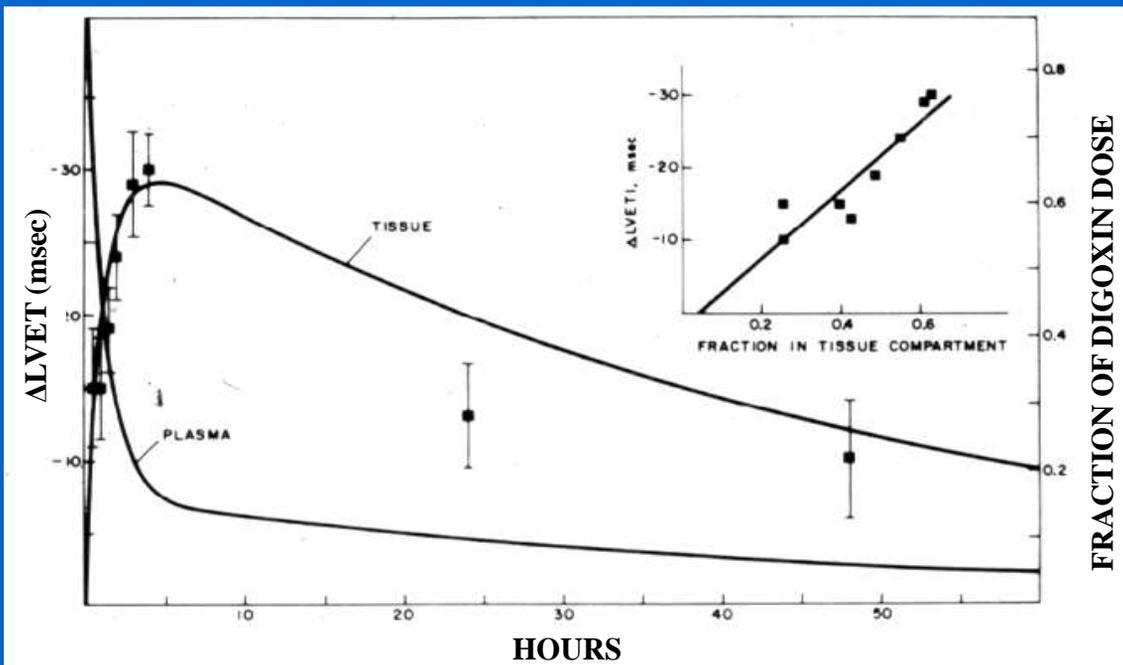
$$V_{d(\text{ss})} = V_1 + V_2 + \dots + V_n$$

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*



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TARGET CONCENTRATION STRATEGY

ESTIMATE INITIAL DOSE

TARGET LEVEL

LOADING DOSE

MAINTENANCE DOSE

**BASED ON CONCEPTS OF
ELIMINATION HALF LIFE
AND CLEARANCE**

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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

1.4 ng/mL

DAILY LOSS
0.25 mg

DIGOXIN CUMULATION

$$.25 \times 2/3 = .17$$

$$\underline{+.25}$$

$$.42 \times 2/3 = .28$$

$$\underline{+.25}$$

$$.53 \times 2/3 = .36$$

$$\underline{+.25}$$

$$.61 \times 2/3 = .41$$

$$\underline{+.25}$$

$$.66 \times 2/3 = .44$$

$$\underline{+.25}$$

$$.69 \times 2/3 = .46$$

$$\underline{+.25}$$

$$.71$$

DOSE #1

DOSE #2

DOSE #3

DOSE #4

DOSE #5

DOSE #6

DOSE #7

CUMULATION FACTOR

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

τ = dose interval

k = elimination rate constant

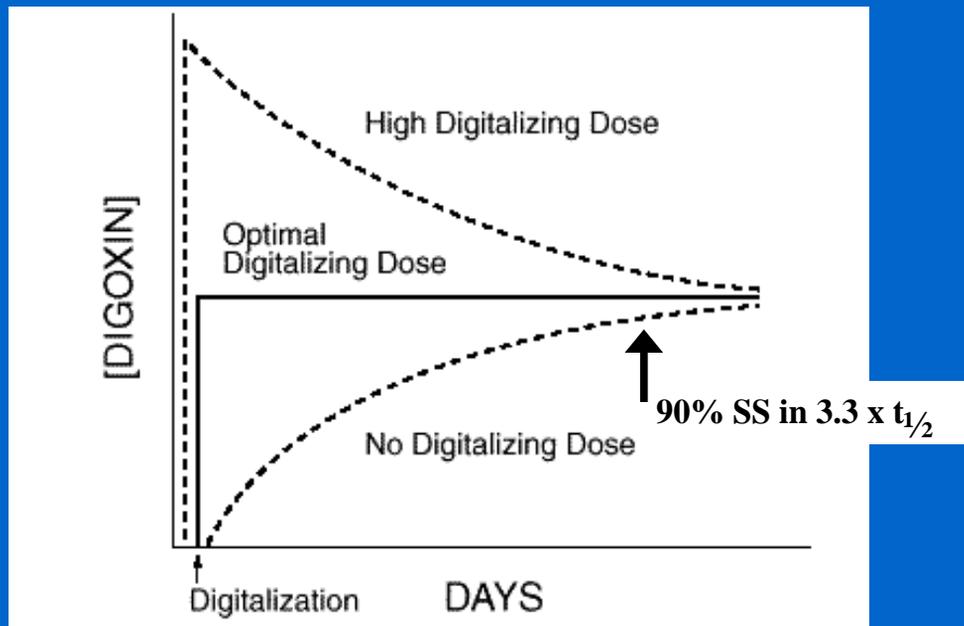
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ELIMINATION RATE CONSTANT

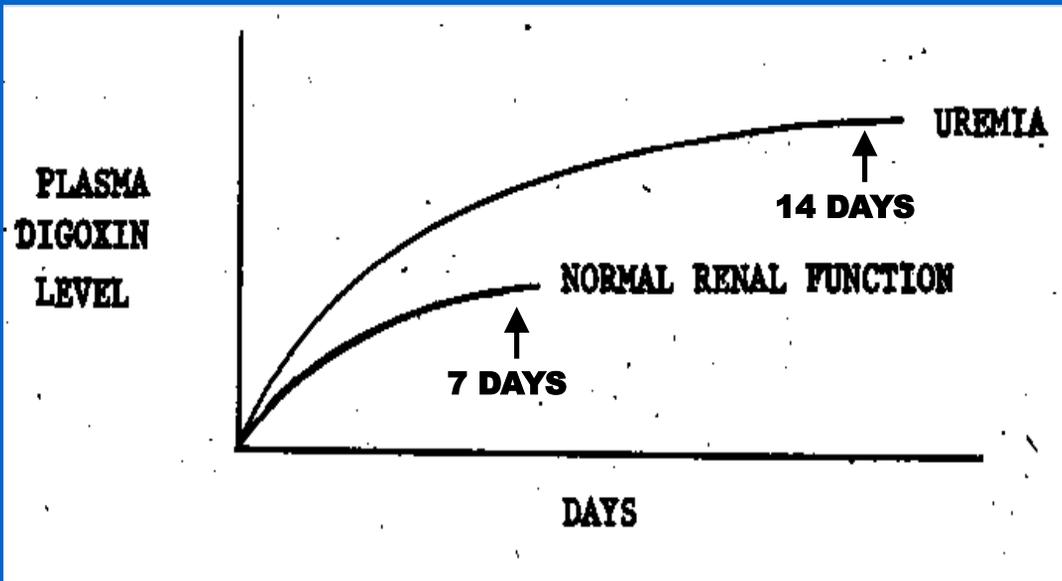
$$k = \frac{0.693}{t_{1/2}}$$

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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.

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



TARGET CONCENTRATION STRATEGY

ESTIMATE INITIAL DOSE

TARGET LEVEL
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MAINTENANCE DOSE



BEGIN THERAPY



ASSESS THERAPY
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 ($k = 0.16 \text{ day}^{-1}$)

TIME TO 90% STEADY STATE:

$3.3 \times 4.3 = 14.2$ days

STEADY STATE PEAK LEVEL:

6.2 ng/mL (post distribution phase)

MEASURED LEVEL:

6.9 ng/mL (pre distribution)

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STEADY STATE CONCENTRATION

CONTINUOUS INFUSION:

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

INTERMITTENT DOSING:

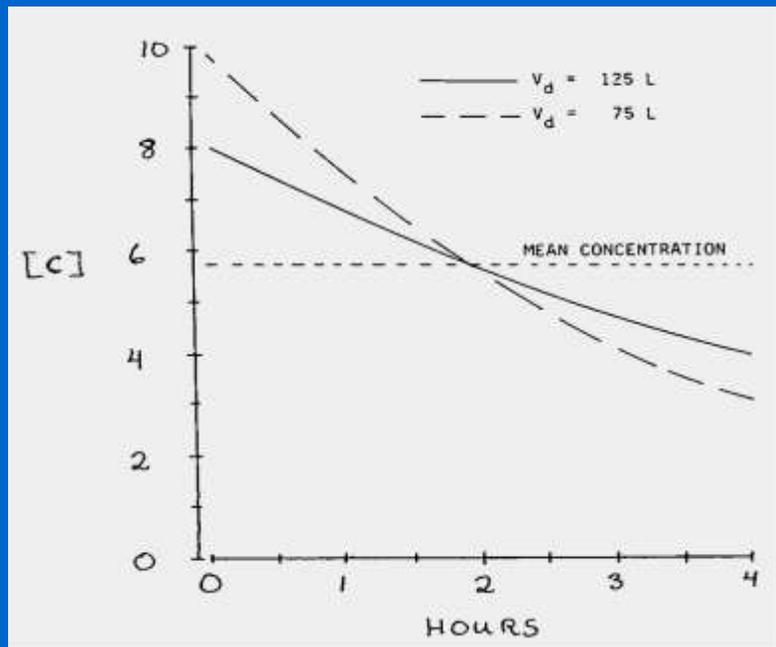
$$\bar{C}_{SS} = \frac{DOSE / \tau}{CL_E}$$



STEADY STATE CONCENTRATION

- *NOT* DETERMINED BY LOADING DOSE
 - MEAN STEADY STATE CONCENTRATION
NOT DETERMINED BY V_d
 - PEAK AND TROUGH *ARE* AFFECTED BY V_d
- 

**V_d AFFECTS PEAK AND TROUGH
BUT NOT MEAN LEVELS**



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

CONTINUOUS INFUSION:

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

INTERMITTENT DOSING:

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

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***



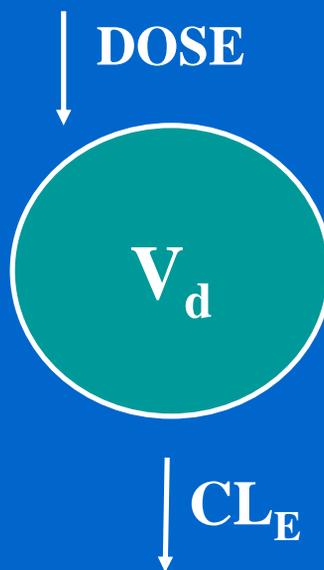
PHARMACOKINETIC MODELS

**WHAT PHARMACOKINETIC
PARAMETERS ARE PRIMARY?**



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SINGLE COMPARTMENT MODEL



ELIMINATION HALF-LIFE

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

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

3 DISTRIBUTION VOLUMES

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

$$V_{d(\text{area})} = \frac{t_{1/2} \cdot \text{CL}_E}{0.693}$$

$$V_{d(\text{ss})} = V_1 + V_2 + \dots + V_n$$

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**SOME DRUGS *NOT* ELIMINATED
BY FIRST ORDER KINETICS**

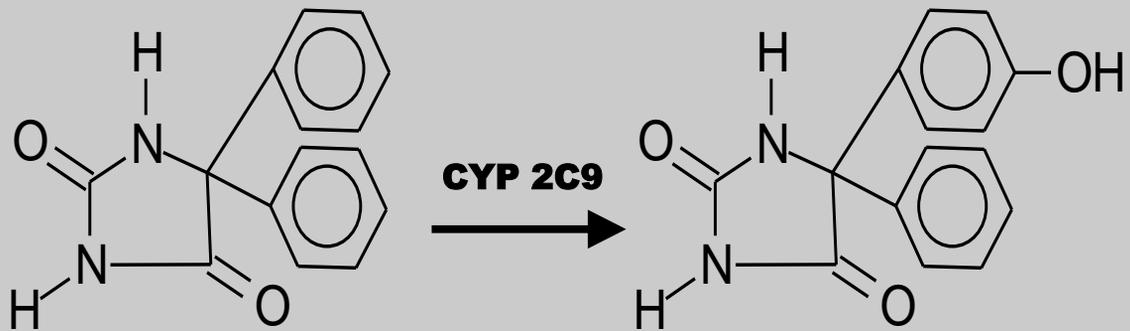
PHENYTOIN (DILANTIN)

ETHYLALCOHOL

ACETYLSALICYLIC ACID (ASPIRIN)

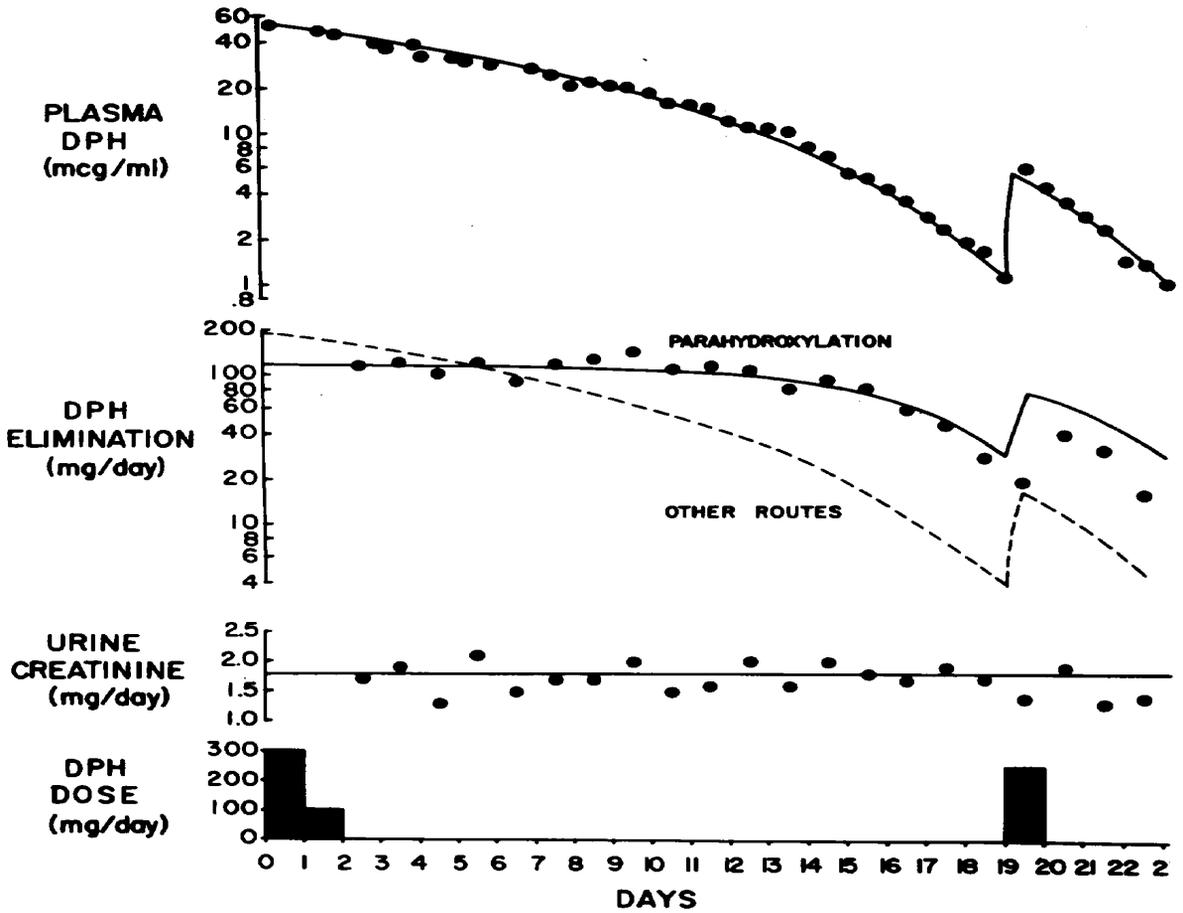
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PHENYTOIN HYDROXYLATION

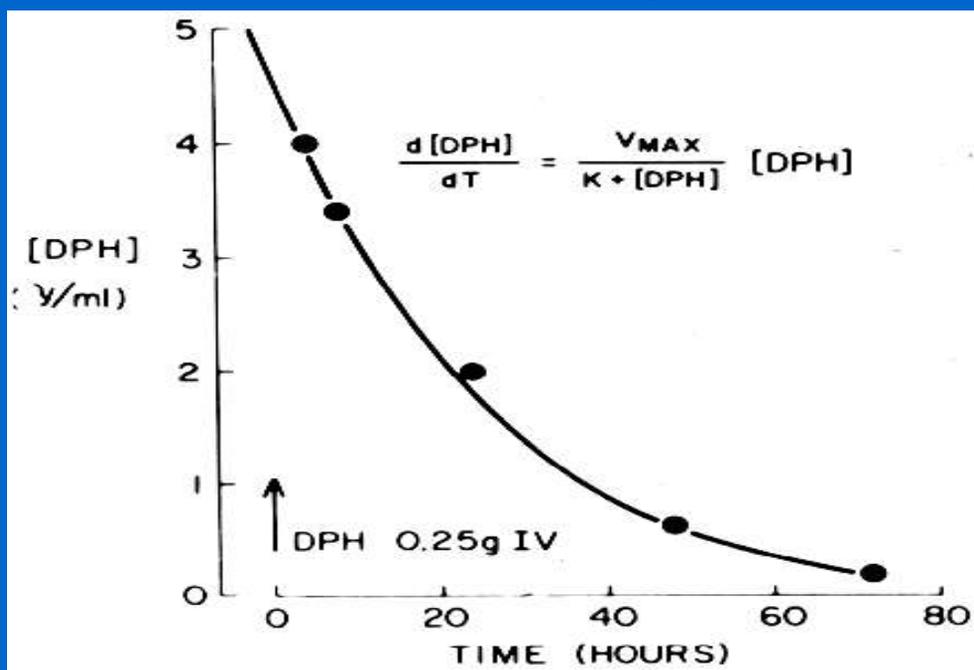


PHENYTOIN

p - HPPH



PHENYTOIN KINETICS in Normal Subjects



STEADY STATE EQUATIONS

FIRST ORDER KINETICS

$$\text{DOSE} / \tau = \text{CL}_{\text{E}} \bullet \bar{\text{C}}_{\text{SS}}$$

MICHAELIS - MENTEN KINETICS

$$\text{DOSE} / \tau = \left[\frac{\text{V}_{\text{max}}}{\text{K}_{\text{m}} + \bar{\text{C}}_{\text{SS}}} \right] \bar{\text{C}}_{\text{SS}}$$

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RELATIONSHIP OF PLASMA LEVEL TO PHENYTOIN DOSE*

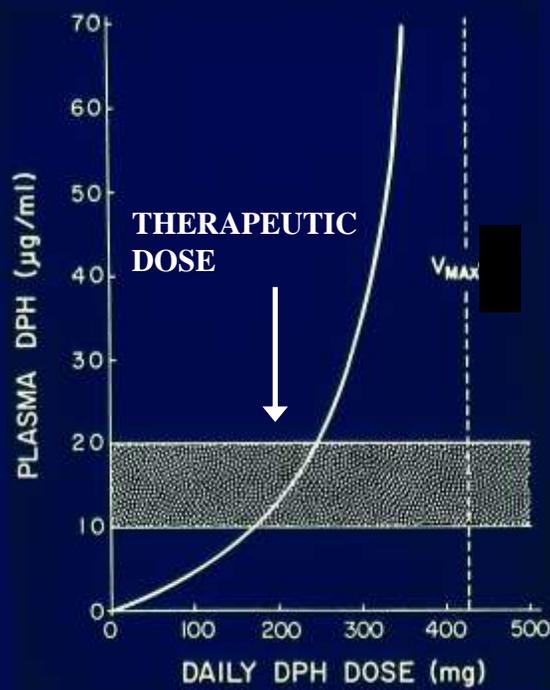
PHENYTOIN DOSE (mg/day)	PLASMA LEVEL µg/mL
300	10
400	20
500	30

(THERAPEUTIC RANGE: 10 – 20 µg/mL)

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

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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 $\mu\text{g}/\text{mL}$. She was sent home on a *reduced* phenytoin dose of 200 mg/day.

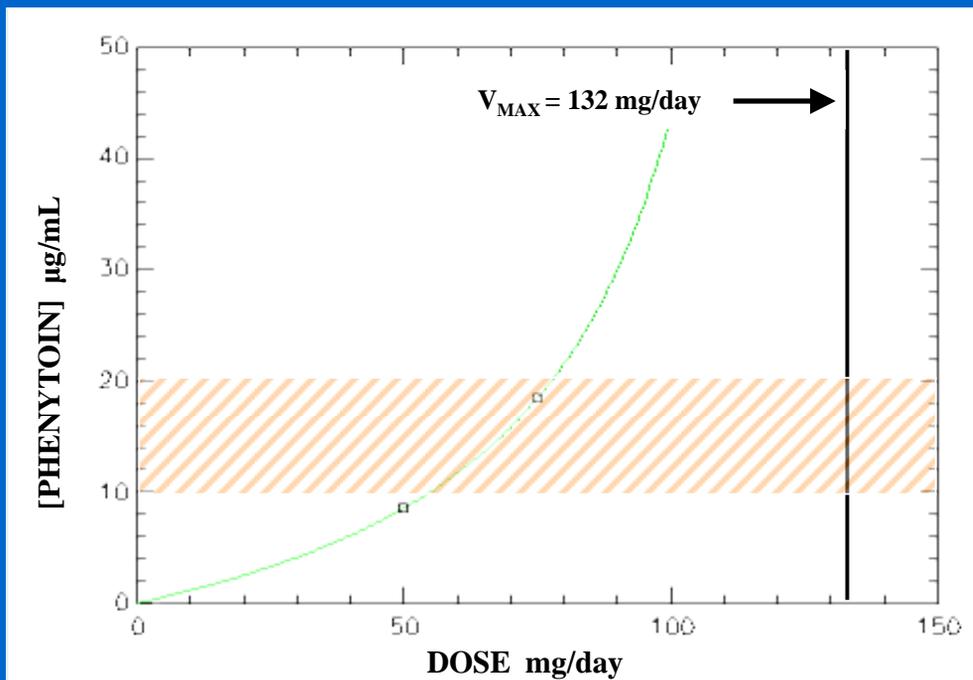


PHENYTOIN CASE HISTORY (cont.)

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 $K_m > C$:

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



PHARMACOKINETICS

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

