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

Down arrow

BEGIN THERAPY

Down arrow

ASSET THERAPY
PATIENT RESPONSE
DRUG LEVEL

Down arrow

REFINE DOSE ESTIMATE – Arrow back to Assess Therapy

ADJUST DOSE (return to Assess Therapy)

RATIONALE FOR
PLASMA LEVEL MONITORING

Flowchart for rationale for plasma level monitoring beginning with Prescribed dose and ending in effect.

FIRST DESCRIPTION OF THERAPEUTIC DRUG MONITORING

Copy of this article from
Wuth O. JAMA
1927;88:2013-17.

RADIOIMMUNOASSAY

Photo of 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

Photo of gas liquid chromatography

HIGH PERFORMANCE
LIQUID CHROMATOGRAPHY

Photo of high performance liquid chromatograph

FLUORESCENCE POLARIZATION IMMUNOASSAY

Photo of TDX FPIA Analyzer

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

Bar chart showing virologic failure rates and percent of adherence rates. Adherence improves treatment outcome.

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*

Chart showing that from Smith TW and Haber E. J Clin Invest 1970;49-2377-86

DIGOXIN: Factors Influencing
OUTCOME in "GREY ZONE"

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

Down Arrow - 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:**	**greater than 3.0 ng/mL**

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

Chart illustrating that from 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 (up arrow) 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

Bar chart showing percent of patients taking four different daily doses of Digoxin from Rathore SS, et al. JAMA 2003,289:871-8

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TARGET LEVEL
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MAINTENANCE DOSE

BASED ON CONCEPT OF DISTRIBUTION VOLUME

DIGOXIN LEVELS after IV Dose

Chart illustrating this showing the distribution phase and the elimination phase

Initial Digitalization

Formula relating initial dose, initial digoxin concentration and apparent volume of distribution.

3 DISTRIBUTION VOLUMES

equation

DISTRIBUTION DELAYS ONSET
of DIGOXIN Chronotropic Action*

Chart

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

DISTRIBUTION DELAYS ONSET of DIGOXIN Inotropic Action*

Chart

Target Concentration Strategy

Estimate initial dose
Target level
Loading dose
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Based on concepts
Elimination half life
and clearance

ELIMINATION HALF-LIFE

<u>ELIMINATION HALF-LIFE</u> 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

EQUATION

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

Maintenance Digoxin Therapy

Formula relating maintenance dose to daily digoxin loss from the body.

DIGOXIN CUMULATION

Formula showing exponential accumulation of digoxin.

CUMULATION FACTOR

equation

τ = dose interval
k = elimination rate constant

ELIMINATION RATE CONSTANT

equation

LOADING & MAINTENANCE **DOSES**

Chart showing Digoxin levels over time as a function of loading and maintenance dosing.

TIME-COURSE OF DIGOXIN CUMULATION

Chart showing plasma Digoxin levels over time.

Steady-state levels take longer to be reached in patients with uremia.

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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PHARMACOKINETIC ANALYSIS OF DIGOXIN CASE HISTORY

***ESTIMATED T1/2*:**

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 equation

Intermittent Dosing equation

STEADY STATE CONCENTRATION

Not determined by loading dose

Mean steady state concentration not determined by Vd

Peak and trough are affected by Vd

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

Chart illustrating this

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

Continuous Infusion equation

Intermittent dosing equation

STEADY STATE CONCENTRATION

NOT **DETERMINED BY LOADING DOSE**

MEAN STEADY STATE CONCENTRATION
NOT **DETERMINED BY Vd**

CHANGES IN MAINTENANCE DOSE
RESULT IN DIRECTLY PROPORTIONAL
CHANGES IN Css FOR MOST DRUGS

PHARMACOKINETIC MODELS

WHAT PHARMACOKINETIC PARAMETERS ARE PRIMARY?

SINGLE COMPARTMENT MODEL

Example diagram

ELIMINATION HALF-LIFE

equation

Therefore, t ½ is t a primary pharmacokinetic parameter

3 *DISTRIBUTION VOLUMES*

equations

Some Drugs are NOT Eliminated by First Order Kinetics

Phenytoin (Dilantin)

Ethyl Alcohol

Acetylsalicylic Acid (aspirin)

Phenytoin Hydroxylation

Chemical structure

Chart

Plasma DPH (mcg/ml)

DPH elimination (mg/day)

Urine Creatine (mg/day)

DPH Dose (mg/day)

Phenytoin Kinetics
In Normal Subjects

Chart depicting Phenytoin Kinetics.

Steady State Equations

First Order Kinetics equation

Michealis – Menten kinetics equation

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

Chart illustrating this.

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 VMAX

Chart depicting this.

BASIS OF *APPARENT* FIRST-ORDER KINETICS

equations

Pharmacokinetics

***PRACTICE PROBLEMS* AT END OF CHAPTER 2**
WITH *ANSWERS* IN APPENDIX II

***EQUATIONS* DERIVED IN "PRINCIPLES OF**
CLINICAL PHARMACOLOGY" TEXTBOOK