COURSE FOCUS

- Scientific basis of drug use, development and evaluation
- Not Therapeutics
- Emphasis is on General Principles for both “old” and “new” drugs

RECOMMENDED TEXT
CLINICAL PHARMACOLOGY

Overview and General Scope

PHARMACOLOGY

The study of drugs and biologics and their actions in living organisms

Drugs: “small molecules”, chemicals

Biologics: “large molecules”, peptides, antibodies
CLINICAL PHARMACOLOGY

THE STUDY OF DRUGS (AND BIOLOGICS) IN HUMANS

Translational Sciences

Knowledge acquired in animal or *in silico* models of disease, *ex-vivo* studies in human tissues, or *in vivo* studies in healthy or diseased humans is *translated* into effective treatment for patients.

*Clinical Pharmacology is a translational discipline essential for rational drug development and therapeutics in humans.*

FOUNDERS OF AMERICAN CLINICAL PHARMACOLOGY

HARRY GOLD  WALTER MODELL
Partial List of GOLD and MODELL Accomplishments

1937 – Introduced Double-Blind Clinical Trial Design *
1939 – Initiated Cornell Conference on Therapy
1953 – Analyzed Digoxin Effect Kinetics to Estimate Absolute Bioavailability as well as Time-Course of Chronotropic Effects†
1960 - Founded Clinical Pharmacology and Therapeutics


PROFESSIONAL GOALS OF CLINICAL PHARMACOLOGISTS

• Discover, develop and evaluate new medicines, regulate their use
• Optimize the use of existing medicines, find new indications
• Define the basis for variability in therapeutic and toxic responses to medicines

Interindividual Variation in Drug Exposure (AUC)

Karim A et al. 2007

[Graph showing the differences in AUC for females and males for different drugs and dosages]
Nortriptyline Drug Exposure
Impact of CYP2D6 Polymorphism


Genetics and Severe Drug Toxicity

HLA-B*5701
Abacavir hypersensitivity
Fluoxacillin liver injury (DILI)

HLA-B*1502
Carbamazepine-induced
Stevens-Johnson syndrome

Adverse Drug Reactions

• Some toxicities can be managed and may be acceptable (risk/benefit ratio) while others are by their nature and severity unacceptable.
• Risk/benefit is contextual (drug and disease).
TORSADES DE POINTES

TERFENADINE METABOLISM*

TERFENADINE (SELDANE)

TERFENADINE CARBOXYLATE (ALLEGRA)


THALIDOMIDE

[Chemical structure of Thalidomide]
Prenatal Drug Exposure: PHOCOMELIA

CONSEQUENCES OF THALIDOMIDE CRISIS

• New FDA Regulations (KEFAUVER-HARRIS 1962 AMENDMENTS)
• Institute of Medicine-National Academy of Sciences review of Therapeutic Claims
• More Research on Causes of ADRs
• NIGMS created Clinical Pharmacology Centers in the USA

Development and Evaluation of New Drugs

• Drug discovery
• Pre-clinical and clinical evaluation
• Post-marketing studies
**Phases of Drug Development**

"Learn and Confirm" Paradigm

*Phase I and II:* The learning phases.
*Phase III:* The confirmatory phase.
*Phase IV:* Postmarketing - learning continues with focus on ADRs and special populations if required.

**Drug Repurposing**

- Finding new biological targets and new therapeutic indications for “old” drugs.
- May shorten drug development time.
- Known human pharmacokinetics.
- Prior human safety data.
Drug Repurposing (C. Austin, NCATS)

Thalidomide: Repurposing

- **Erythema Nodosum Leprosum**
  - Astute clinical observation of benefit
- **Multiple Myeloma**
  - Targeted development

These are FDA-approved indications
(immunomodulatory agent)

Marketing done under a special restricted distribution program:
*System for Thalidomide Education and Prescribing Safety (S.T.E.P.S.)*

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Novel FDA-Approved Indications for “Repurposed Drugs”

- **Apomorphine** - Parkinson’s Disease
- **Sildenafil** - Pulmonary Hypertension
- **Taxotere** - Prostate Cancer
- **Lamotrigine** - Bipolar Disorder
- **Bevacizumab** - Lung Cancer (non-SQ, non-SCLC)
- **Hydroxyurea** - Sickle Cell Disease
- **Minoxidil** - Scalp hair re-growth (vertex in men)

Source: Product label (package insert)
Pharmacokinetics (PK)

Introduction

Clinical Pharmacokinetics

---

**PHARMACOKINETICS**

The *QUANTITATIVE ANALYSIS* of the *TIME COURSE* of DRUG

**ABSORPTION, DISTRIBUTION, METABOLISM, and EXCRETION**

---

Pharmacokinetics - Pharmacodynamics

- Prescribed Dose
- Adherence
- Absorption
- Protein Bound
- Plasma Free
- Elimination
- Metabolism
- Renal Excretion
- Most Tissues Non Specific Binding
- Distribution
- Biophase Receptor Binding
- Effect
USES OF PHARMACOKINETICS

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

Dose – Response Relationship

- A central tenet of pharmacology
- The careful study of “drug exposure – response” relationships is aimed at finding “the right dose” for a given therapeutic indication
- “Exposure – response” applies to both drug efficacy and toxicity
- PK/PD modeling approaches

“Target concentration” strategy

- Based on observed individual variation in drug exposure (AUC) when using “standard” doses.
- Attempts to “individualize” therapy when therapeutic and toxic ranges of drug concentrations in plasma have been established.
- Optimize efficacy, minimize toxicity.
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

DRUG CANDIDATES FOR TDM

• Low therapeutic index

• No physiologic endpoints or biomarkers to guide dosage

• Pharmacokinetics vary widely between individuals

• Need to monitor adherence?

FIRST DESCRIPTION OF THERAPEUTIC DRUG MONITORING

TARGET CONCENTRATION STRATEGY

ESTIMATE INITIAL DOSE
TARGET LEVEL
LOADING DOSE
MAINTENANCE DOSE

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

**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**


---

**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

**Question:** Doses of digoxin used in this study should have resulted in higher levels? **Study limitation:** No digoxin levels done after one month in study (patients seen for 48 months).
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.

DISTRIBUTION PHASE | ELIMINATION PHASE

SINGLE COMPARTMENT MODEL

DOSE

\( V_d \)

\( \text{CL}_E \)
3 DISTRIBUTION VOLUMES

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

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

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

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

DISTRIBUTION DELAYS ONSET

of DIGOXIN Chronotropic 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

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

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

\[ t_{1/2} = \text{elimination half life} \]

\[ k = \text{elimination rate constant} \]

\[ CL_E = \text{elimination clearance} \]
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 mg/mL

DAILY LOSS
0.25 mg

DIGOXIN CUMULATION

25 x 2/3 = .17
+ .25
.42 x 2/3 = .28
+ .35
.53 x 2/3 = .36
+ .25
.64 x 2/3 = .41
+ .35
.66 x 2/3 = .44
+ .25
.69 x 2/3 = .46
+ .25
.71

CUMULATION FACTOR

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

\[ \tau = \text{dose interval} \]
\[ k = \text{elimination rate constant} \]
**ELIMINATION RATE CONSTANT**

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

**LOADING & MAINTENANCE DOSES**

90% SS in 3.3 \( t^{1/2} \) days

**TIME-COURSE OF DIGOXIN CUMULATION**

Plasma Digoxin Level

- Normal Renal Function (7 days)
- Uremia (14 days)
Introduction to Clearance

- **Clearance** is a “primary” parameter in the pharmacokinetic analysis of drug distribution and elimination.

- Understanding the concept of clearance is essential for drug evaluation and use in clinical medicine.

CREATININE CLEARANCE EQUATION

\[ CL_{Cr} = \frac{U \times V}{P} \]

- \( U \) = Urine concentration
- \( V \) = Urine volume/time
- \( P \) = Plasma concentration

CREATININE CLEARANCE REVISITED

**RATE OF APPEARANCE OF Cr IN URINE** (\( dE/dt \)):
\[ dE/dt = CL_{Cr} \times P \]

**RATE OF CHANGE OF Cr IN BODY** (\( dX/dt \)):
\[ dX/dt = [\] \times CL_{Cr} \times P \]

**STATE STEADY AT**:
\[ P = \frac{1}{CL_{Cr}} \]

\( I = \) RATE OF CREATININE SYNTHESIS
**STEADY STATE CONCENTRATION**

**CONTINUOUS CREATININE SYNTHESIS:**
\[ C_{SS} = \frac{I}{CL_{Cr}} \]

**CONTINUOUS DRUG INFUSION:**
\[ C_{SS} = \frac{I}{CL_{E}} \]

**COCKCROFT & GAULT EQUATION***

\[ CL_{Cr} = \frac{(140 - \text{age}) \times \text{weight in kg}}{72 \times \text{serum Cr in mg/dL}} \]

[reduce estimate by 15% for women]


**Terms in red estimate creatinine synthesis rate.**

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RENAL FUNCTION IN PATIENTS TOXIC FROM DIGOXIN*

<table>
<thead>
<tr>
<th>SERUM Cr (mg %)</th>
<th>Clcr (mL/min)</th>
<th>≥ 50</th>
<th>&lt; 50</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 1.7</td>
<td>4</td>
<td>19</td>
<td>52%</td>
</tr>
<tr>
<td>&gt; 1.7</td>
<td>0</td>
<td>21</td>
<td>48%</td>
</tr>
</tbody>
</table>


MDRD Study Equation

- Modification of Diet in Renal Disease (MDRD)
- *This equation (many versions) provides an estimate of glomerular filtration rate (eGFR) normalized to body surface area (ml/min/1.73 m²)*
- To be discussed in lecture on PK alterations in renal disease

CKD-EPI Collaboration Equation

- Chronic Kidney Disease (CKD) Epidemiology Collaboration Equation
- *More accurate than MDRD equation in estimating GFR (eGFR)*
- *Less bias if GFR >60 ml/min/1.73 m²*
- To be discussed in lecture on PK alterations in renal disease
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
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

FOR MOST DRUGS, C_ss IS PROPORTIONAL TO DOSE (Dosing Rate)

CONTINUOUS INFUSION:

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

INTERMITTENT DOSING:

\[ C_{ss} = \frac{DOSE}{\tau \cdot CL_e} \]

SOME DRUGS NOT ELIMINATED BY FIRST ORDER KINETICS

PHENYTOIN (DILANTIN)
ETHYLALCOHOL
ACETYLSALICYLIC ACID (ASPIRIN)
PHENYTOIN HYDROXYLATION

PHENYTOIN p-HPPH

CYP 2C9

SATURATION OF DPH HYDROXYLATION

PHENYTOIN KINETICS in Normal Subjects
STEADY STATE EQUATIONS

FIRST ORDER KINETICS
\[ \text{DOSE} / \tau = \text{CL}_E \cdot \bar{C}_{\text{SS}} \]

MICHAELIS - MENTEN KINETICS
\[ \text{DOSE} / \tau = \frac{V_{\text{max}}}{K_m + \bar{C}_{\text{SS}}} \bar{C}_{\text{SS}} \]

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

THERAPEUTIC DOSE

THRESHOLD

0 10 20 30 40 50 60 70

PLASMA CONCENTRATION (µg/mL)

0 100 200 300 400 500

DAILY PHENYTOIN DOSE (mg)
BASIS OF APPARENT FIRST-ORDER KINETICS

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

If \( K_m > C \):

\[ \frac{dC}{dt} = \left( \frac{V_{\max}}{K_m} \right) C = k' C \]

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PHARMACOKINETICS

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

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Historical Overview

The establishment of experimental pharmacology as a discipline in Europe and the USA in the 19th and 20th centuries.
John Jacob Abel

“Father of American Pharmacology”

- First full-time Professor in Materia Medica and Therapeutics at the University of Michigan (1891)
- Founder, “Journal of Pharmacology and Experimental Therapeutics” (1896)

John Jacob Abel

Crystallization of insulin
Research on tetanus toxin
Study of the phthaleins
Invention of the artificial kidney (vivodialysis or vividiffusion)

Oswald Schmiedeberg

Professor of Pharmacology at Strassbourg (1872)

Pioneer studies on autonomic nervous system, nicotine, muscarine

Chloroform blood levels
Rudolph Bucheim

Professor at the University of Dorpat (now Tartu, Estonia) (1847-1867).

Established the first experimental pharmacology laboratory in search for proof of drug actions.

LINEAGE of Modern Clinical Pharmacology

PATER FAMILIAS
RUDOLPH BUCHEIM

FOUNDING FATHERS
US
HARRY GOLD
WALTER MODELL
EUROPE
PAUL MARTINI

RENAISSANCE LEADERS
US
KEN MELMON
LEON GOLDBERG
JOHN OATES
DAN AZARNOFF
EUROPE
FOLKE SJÖQUIST
LOU LAGNÁ
COLLIN DOLLEY
<table>
<thead>
<tr>
<th>HISTORY OF CLINICAL PHARMACOLOGY</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Albert Sjoerdsma, M.D., Ph.D.</strong></td>
</tr>
<tr>
<td>Experimental Therapeutics Branch</td>
</tr>
<tr>
<td>National Heart Institute (1958-1971)</td>
</tr>
<tr>
<td><em>Lou Gillespie, John Oates, Leon Goldberg, Richard Crout, Ken Melmon</em></td>
</tr>
<tr>
<td>Serotonin, carcinoid syndrome, antidepressant drugs</td>
</tr>
<tr>
<td>Pheochromocytoma, antihypertensive drugs</td>
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</tbody>
</table>