COURSE FOCUS

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

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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 – Analized Digoxin Effect Kinetics to Estimate Absolute Bioavailability as well as Time-Course of Chronotropic Effects†

1960 - Founded Clinical Pharmacology and Therapeutics

HISTORY OF CLINICAL PHARMACOLOGY

Albert Sjoerdsma, M.D., Ph.D.
Experimental Therapeutics Branch
National Heart Institute (1958-1971)
Lou Gillespie, John Oates, Leon Goldberg, Richard Crout, Ken Melmon
Serotonin, carcinoid syndrome, antidepressant drugs
Pheochromocytoma, antihypertensive drugs
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
Figure 3. Body weight- and dose-adjusted arithmetic mean (−) and individual values for pioglitazone (left panel) and metformin (right panel) AUC, in females and males following single oral doses of commercial pioglitazone (15 mg) and metformin (500 mg or 850 mg) tablets given together to young healthy subjects.
Nortriptyline Drug Exposure

Impact of CYP2D6 Polymorphism

Genetics and Severe Drug Toxicity

**HLA-B*5701**
Abacavir hypersensitivity
Flucoxacillin 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*

THALIDOMIDE
Prenatal Drug Exposure:
PHOCOMELIA
CONSEQUENCES OF THALIDOMIDE CRISIS

- New FDA Regulations
  \(KEFAUVER-HARRIS 1962 AMENDMENTS\)
- Institute of Medicine-National Academy of Sciences \textit{review of Therapeutic Claims}
- More Research on \textit{Causes} of ADRs
- NIGMS created \textit{Clinical Pharmacology Centers} in the USA
Development and Evaluation of New Drugs

• Drug discovery
• Pre-clinical and clinical evaluation
• Post-marketing studies
PHASES OF PRE-MARKETING DRUG DEVELOPMENT

IND
- Chemical Synthesis and Formulation Development
- Animal Models for Efficacy
  - Assay Development
  - Animal PK and PD
- Animal Toxicology

Pre-Clinical Development

PHASE I
- Dose Escalation and Initial PK

PHASE II
- Proof of Concept and Dose Finding
- PK and PD Studies in Special Populations

Clinical Development

PHASE III
- Large Efficacy Trials with PK Screen

NDA
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)

>400,000 compounds, 10 yrs

Target ➔ Screen ➔ Test chemicals on target ➔ Lead Product ➔ GMP ➔ Preclinical Trials ➔ Clinical Trials ➔ FDA approval

1-2 years?

3000 drugs
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.)*
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
The QUANTITATIVE ANALYSIS of the TIME COURSE of DRUG ABSORPTION, DISTRIBUTION, METABOLISM, and EXCRETION
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

First Academic Hospital
Clinical Drug Analysis Lab

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

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

New Therapeutic Range: 0.5 - 0.9 ng/mL

Benefit results from \textit{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 I.V.

DIGOXIN CONCENTRATION (ng/ml)

DISTRIBUTION PHASE | ELIMINATION PHASE

HOURS

0.2  0.4  0.6  0.8  1.0  1.2  1.4  1.6  1.8  2.0  2.2  2.4

0  2  4  6  8  10  12  14  16  18  20  22  24
SINGLE COMPARTMENT MODEL

\[ \text{DOSE} \downarrow \]

\[ V_d \]

\[ \downarrow \text{CL}_E \]
3 DISTRIBUTION VOLUMES

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

\[
V_{d \text{ (area)}} = \frac{t \cdot CL_E}{0.693}
\]

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

DIGITALIZING DOSE
0.75 mg = 750 x 10³ 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

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

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

\[ CL_E = k \times V_d \]

- \( t_{1/2} \) = 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 x 2/3 = .17
  +.25
  .42 x 2/3 = .28
  +.25
  .53 x 2/3 = .36
  +.25
  .61 x 2/3 = .41
  +.25
  .66 x 2/3 = .44
  +.25
  .69 x 2/3 = .46
  +.25
  .71

DOSE #1
DOSE #2
DOSE #3
DOSE #4
DOSE #5
DOSE #6
DOSE #7
CUMULATION FACTOR

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

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

\[ k = \frac{0.693}{t_{1/2}} \]
LOADING & MAINTENANCE DOSES

90% SS in 3.3 x t₁/₂
TIME-COURSE OF DIGOXIN CUMULATION

- Plasma Digoxin Level
- Days
- Uremia
- Normal Renal Function
- 14 Days
- 7 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

\[ \text{CL}_{\text{Cr}} = \frac{U \times V}{P} \]

- \( U \) = 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) :
\[ dX/dt = I - CL_{Cr} \times P \]

AT STEADY STATE :
\[ P = I / CL_{Cr} \]

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*

\[
CL_{Cr} = \frac{(140 - \text{age})(\text{weight in kg})}{72 (\text{serum Cr in mg/dL})} \\
\text{[reduce estimate by 15% for women]}
\]

COCKCROFT & GAULT EQUATION

\[ \text{CL}_{\text{Cr}} = \frac{\text{I}}{\text{P}} \]

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

[reduce estimate by 15% for women]

Terms in red estimate creatinine synthesis rate.
**RENAL FUNCTION IN PATIENTS TOXIC FROM DIGOXIN**

<table>
<thead>
<tr>
<th>SERUM Cr (mg %)</th>
<th>Cl(_{\text{Cr}}) (mL/min)</th>
<th>≥ 50</th>
<th>&lt; 50</th>
<th>52%</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 1.7</td>
<td>4</td>
<td>19</td>
<td></td>
<td>52%</td>
</tr>
<tr>
<td>&gt; 1.7</td>
<td>0</td>
<td>21</td>
<td></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:

\[
\bar{C}_{ss} = \frac{DOSE/\tau}{CL_E}
\]
SOME DRUGS NOT ELIMINATED BY FIRST ORDER KINETICS

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

CYP 2C9

PHENYTOIN $\rightarrow p$-HPPH
SATURATION OF DPH HYDROXYLATION
PHENYTOIN KINETICS in Normal Subjects

\[ \frac{d[DPH]}{dT} = \frac{V_{\text{MAX}}}{K \times [DPH]} [DPH] \]

[Graph showing the concentration of DPH over time post intravenous administration of 0.25g.]
STeady State Equations

**First Order Kinetics**

\[
\frac{\text{Dose}/\tau}{\text{Cl}_E \cdot \bar{C}_{\text{SS}}}
\]

**Michaelis-Menten Kinetics**

\[
\frac{\text{Dose}/\tau}{\left[ \frac{V_{\text{max}}}{K_m + \bar{C}_{\text{SS}}} \right] \bar{C}_{\text{SS}}}
\]
<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
**BASIS OF APPARENT FIRST-ORDER KINETICS**

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

If \( K_m > C \):

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

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

• **EQUATIONS** DERIVED IN “PRINCIPLES OF
  CLINICAL PHARMACOLOGY” TEXTBOOK
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
(vividialysis 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
LINEAGE OF Modern Clinical Pharmacology

PATER FAMILIAS
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US
KEN MELMON
LEON GOLDBERG
JOHN OATES
DAN AZARNOFF
EUROPE
FOLKE SJÖQVIST