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
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
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

TERFENADINE (SELDANE)

TERFENADINE CARBOXYLATE (ALLEGRA)


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, NHGRI)

1-2 years?

>400,000 compounds, 10 yrs

Target

Screen

Test chemicals on target

Lead

Product

Preclinical

Lead

Clinical

Marketed

Thalidomide: Therapeutic Uses

• Erythema Nodosum Leprosum
  Astute clinical observation

• 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.)

Pharmacokinetics (PK)

Introduction

Clinical Pharmacokinetics
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 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 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

SINGLE COMPARTMENT MODEL

\[ V_d \]
\[ \text{DOSE} \]
\[ \text{CL}_E \]

3 DISTRIBUTION VOLUMES

\[ V_{d (\text{extrap.})} = \frac{\text{DOSE}}{C_0} \]
\[ V_{d (\text{area})} = \frac{t_{1/2} \cdot \text{CL}_E}{0.693} \]
\[ V_{d (ss)} = V_1 + V_2 + \ldots + V_n \]
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**

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

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

\[
CL_E = k \times V_d
\]

- \( t_{1/2} \) = elimination half life
- \( k \) = elimination rate constant
- \( CL_E \) = elimination clearance

---

**MAINTENANCE DIGOXIN THERAPY**

**MAINTENANCE DOSE**

0.25 mg

**NORMAL DAILY LOSS:**

\[= \frac{1}{3} \text{ Total Body Stores} = \frac{1}{3} \times (0.75) \, \text{mg} = 0.25 \, \text{mg}\]

**DAILY LOSS**

0.25 mg

1.4 ng/mL
**DIGOXIN CUMULATION**

Dose #1

\[ 0.25 \times \frac{2}{3} = 0.17 \]

\[ + 0.25 \]

\[42 \times \frac{2}{3} = 0.28 \]

Dose #2

\[ 0.25 \]

\[53 \times \frac{2}{3} = 0.36 \]

\[ + 0.25 \]

\[61 \times \frac{2}{3} = 0.41 \]

Dose #3

\[ 0.25 \]

\[66 \times \frac{2}{3} = 0.44 \]

\[ + 0.25 \]

\[69 \times \frac{2}{3} = 0.46 \]

Dose #4

\[ 0.25 \]

\[71 \]

Dose #5

\[ 0.25 \]

\[78 \]

Dose #6

\[ 0.25 \]

\[84 \]

Dose #7

\[ 0.25 \]

\[89 \]

**CUMULATION FACTOR**

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

\( \tau = \text{dose interval} \)

\( k = \text{elimination rate constant} \)

**ELIMINATION RATE CONSTANT**

\[
k = \frac{0.693}{t_{1/2}}
\]
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 (\(dX/dt\)):
\[ dX/dt = I - CL_{Cr} \times P \]

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*  

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

[reduce estimate by 15% for women]  


COCKCROFT & GAULT EQUATION  

\[ \text{CL}_{\text{Cr}} = \frac{\frac{1}{P}}{ } \]  

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

[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>( \text{CL}_{\text{Cr}} ) (mL/min)</th>
<th>( \geq 50 )</th>
<th>&lt; 50</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \leq 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)
• To be discussed in lecture on PK alterations in renal disease

STEADY STATE CONCENTRATION

CONTINUOUS INFUSION:

$$C_{ss} = \frac{1}{CL_E}$$

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**

![Graph showing the effect of V_d on peak and trough concentrations]

**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

[Diagram of phenytoin hydroxylation]

**CYP 2C9**

PHENYTOIN $p$-HPPH

[Graph showing plasma DPH, DPH elimination, and DPH dose over days]
PHENYTOIN KINETICS in Normal Subjects

Steady State Equations

First Order Kinetics

\[
\frac{\text{DOSE}}{\tau} = \frac{\text{CL}}{\tau} \cdot \overline{C}_{\text{SS}}
\]

Michaelis-Menten Kinetics

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

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

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

- Review Textbook Chapters 1 and 2
- 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

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WALTER MOORELL
EUROPE
PAUL MARTINI

RENAISSANCE LEADERS
US
KEN MELMON
LEON GOLDBERG
JOHN OATES
DAN AZARNOFF
EUROPE
FOLKE SJÖQVIST
JAN KOCH-WESER
LOU LAGNANA
COLIN DOLLEY

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