Principles of Clinical Pharmacology

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Office of Clinical Research Training
and Medical Education
National Institutes of Health
Clinical Center
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Lipsett Amphitheater
Principles of Clinical Pharmacology
Remote Sites 2011 - 2012

Cincinnati’s Children’s Hospital Medical Center
Duke University Medical Center, Durham
University of California, Los Angeles
Harbor-UCLA Medical Center, Los Angeles
Akron’s Children Hospital
Wayne State University, Detroit
Indiana University, Indianapolis
BARDA-HHS, Washington DC
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Remote Sites 2011-2012

University of North Carolina, Chapel Hill
Howard University, Washington DC
Walter Reed Army Institute of Research and USUHS, Silver Spring, Maryland
University of Iowa, Iowa City
Eli Lilly and Company, Indianapolis
Johnson and Johnson, San Diego
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Remote Sites 2011-2012

Comprehensive Clinical Development
Tacoma, Washington - Miramar, Florida
Daiichi Sankyo, Inc., Edison, New Jersey
University of Utah, Salt Lake City, Utah
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Remote Sites 2011-2012

NCI - Frederick, Maryland
NIA - Baltimore, Maryland
NIDA - Baltimore, Maryland
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International Sites 2011-2012

JSS University, Mysore, India
National Academy of Medicine, Buenos Aires, Argentina
Erasmus University Medical Center, Rotterdam, the Netherlands
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CIDEIM
Cali, Colombia
Fundacion Valle del Lili
Cali, Colombia
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Dong-A Medical College
Busan, South Korea
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Our Colleagues at:
Medical Arts and Events Management
Center for Information Technology
Adobe Connect Web Team
Clinical Center/OD Communications
d’Vinci Interactive – Registration Database (contractor)
Quotient – Website (contractor)
COURSE MODULES

MODULE 1: Pharmacokinetics
MODULE 2: Drug metabolism and Transport
MODULE 3: Assessment of Drug Effects
MODULE 4: Optimizing and Evaluating Therapy
MODULE 5: Drug Discovery and Development
RECOMMENDED TEXT

PRINCIPLES OF CLINICAL PHARMACOLOGY
SECOND EDITION

Arthur J. Atkinson, Jr., Darrell R. Abernethy, Charles E. Daniels, Robert Dedrick and Sanford P. Harkey
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
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.*
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
CAREER GOALS OF CLINICAL PHARMACOLOGISTS

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

• Scientific basis of drug use, development and evaluation
• *Not* Therapeutics
• Emphasis is on *General Principles* for both “old” and “new” drugs
“Introduction” Lecture Outline

- Historical overview
- The problem of adverse drug reactions (ADRs)
- Drug discovery and development
- Variability in drug responses
- Introduction to pharmacokinetics
- The concept of clearance
The establishment of *experimental pharmacology* as a discipline in Europe and the USA in the 19\textsuperscript{th} and 20\textsuperscript{th} centuries.
JOHN JACOB ABEL
1857 - 1938
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
1838 - 1921
Oswald Schmiedeberg

Professor of Pharmacology at Strassbourg (1872)

Pioneer studies on autonomic nervous system, nicotine, muscarine

Chloroform blood levels
RUDOLPH BUCHEIM
1820 - 1879
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.
LACK OF IMPORTANCE ATTACHED TO DRUG THERAPY

“Fortunately a surgeon who uses the wrong side of the scalpel cuts his own fingers and not the patient; if the same applied to drugs they would have been investigated very carefully a long time ago.”

*Placing emphasis on therapeutic technique and rational prescribing*

Rudolph Bucheim
*Beiträge zur Arzneimittellehre, 1849*
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

LINEAGE of Modern Clinical Pharmacology

PATER FAMILIAS
RUDOLPH BUCHEIM

FOUNDING FATHERS

US
HARRY GOLD
WALTER MODELL

EUROPE
PAUL MARTINI
Adverse Drug Reactions

• We need to develop drugs that are both effective and safe.
• 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).
CHARACTERISTICS OF MOST ADRs*

• MOST NOT CAUSED BY NEW DRUGS
• MOST NOT IDIOSYNCRATIC REACTIONS
• ~ 80% ARE RELATED TO DRUG DOSE

“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.
SERIOUS ADVERSE DRUG REACTION: An adverse drug reaction (ADR) that requires or prolongs hospitalization, is permanently disabling or results in death.

A concern with both investigational drugs and marketed drugs.
A modern example - Cytokine Storm (1)

“Six healthy young male volunteers at a contract research organization were enrolled in the first phase I clinical trial of TGN1412, a novel superagonist anti-CD28 monoclonal antibody that directly stimulates T cells.

A modern example - Cytokine Storm (2)

Within 90 minutes after receiving a single intravenous dose...all six volunteers had a systemic inflammatory response...rapid induction of proinflammatory cytokines...headache, myalgias, nausea, diarrhea, erythema, vasodilatation, and hypotension. Within 12 to 16 hours they became critically ill...

All six patients survived.”

A modern example – Cytokine storm (3)

Preclinical models *did not predict* the risk of this reaction!

Simultaneous *first-in-human dosing* in 6 volunteers also a problem.
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
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 SJÖQVIST
HISTORY OF CLINICAL PHARMAKOLOGY

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
Development and Evaluation of New Drugs

- Drug discovery
- Pre-clinical and clinical evaluation
- Post-marketing studies
MEDICINES “DISCOVERED” BY CLINICAL INVESTIGATORS

**NEW INDICATION:**
- ALLOPURINOL (Gout) - *RW Rundles*

**ENDOGENOUS COMPOUND:**
- DOPAMINE (Shock) - *LI Goldberg*

**DRUG METABOLITE:**
- FEXOFENADINE (Antihistamine) - *RL Woosley at al.*
ALLOPURINOL

MEDICINES “DISCOVERED” BY CLINICAL INVESTIGATORS

NEW INDICATION:
ALLOPURINOL (Gout) - RW Rundles

ENDOGENOUS COMPOUND:
DOPAMINE (Shock) - LI Goldberg

DRUG METABOLITE:
FEXOFENADINE (Antihistamine) - RL Woosley et al.
DOPAMINE

MEDICINES “DISCOVERED” BY CLINICAL INVESTIGATORS

NEW INDICATION:
ALLOPURINOL (Gout) - RW Rundles

ENDOGENOUS COMPOUND:
DOPAMINE (Shock) - LI Goldberg

DRUG METABOLITE:
FEXOFENADINE (Antihistamine) - RL Woosley et al.
TORSADES DE POINTES
TERFENADINE METABOLISM*

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

Clinical Development

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

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, NHGRI)

1-2 years?

>400,000 compounds, 10 yrs

3000 drugs

FDA approval

Target → Screen → Test chemicals on target → Lead Product → GMP → Preclinical → Clinical Trials
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.)*
Variability in Drug Response

• Pharmacokinetic (PK) basis
• Pharmacodynamic (PD) basis

Both PK and PD variability may be due to *genetic* and/or *environmental* factors.
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.

44 • J Clin Pharmacol 2007;47:37-47
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
Introduction to Pharmacokinetics

• This will be the subject of *Module 1* in our course.

• *Essential* for integration of material in subsequent course modules.
PHARMACOKINETICS

The QUANTITATIVE ANALYSIS of the TIME COURSE of DRUG ABSORPTION, DISTRIBUTION, METABOLISM, and EXCRETION
RATIONALE FOR PLASMA LEVEL MONITORING

PREScribed DOSE

ADHERENCE

ABSORPTION

PROTEIN BOUND

PLASMA

FREE

ELIMINATION

METABOLISM

RENAL EXCRETION

MOST TISSUES NONSPECIFIC BINDING

DISTRIBUTION

BIOPHASE RECEPTOR BINDING

EFFECT
DRUG DOSE SELECTION

TRADITIONAL:

Look up “usual” dose in PDR
Memorize “usual” dose

IMPROVED:

Individualize dosing

Apply pharmacokinetics and the “target concentration strategy”
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***

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

[reduce estimate by 15% for women]

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.
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
### 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>
<th>Overall %</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\leq 1.7$</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>

ESTIMATED $Cl_{Cr}$

- *ESSENTIAL* for safe and effective use of *renally* eliminated drugs

- Important *PREREQUISITE* for application of pharmacokinetic principles

- Need to automate - *BUT*:
  - Laboratory system often does not “talk” with patient database
  - Patients often not weighed
PATHOPHYSIOLOGIC FACTORS NOT ACCOUNTED FOR IN DRUG DOSING

* Lesar TS, Briceland L, Stein DS. JAMA 1997;277:312-7.