Principles of Clinical Pharmacology
Juan J.L. Lertora, M.D., Ph.D.
Director
Clinical Pharmacology Program

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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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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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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Dong-A Medical College
Busan, South Korea
Inha University Hospital
Incheon, South Korea
Instituto Nacional de Enfermedades Neoplasicas (INEN), Lima, Peru
PCP Course Team – OCRTME

LaTanya Bailey
Course Cordinator
301-435-6618
baileyla@mail.nih.gov

Avril Bertrand
Benita Bazemore
PCP Course Team

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


Photo of Book Cover
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.
Dose – Response Relationship

A central tenet of pharmacology

The careful study of “drug exposure – response” relationships is central to 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
Historical Overview

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

Photo of John Jacob Abel in a laboratory.
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
(vividualysis or vividiffusion)
OSWALD SCHMIEDEBERG
1838 – 1921

Photo of Oswald Schmiedeberg
Oswald Schmiedeberg

Professor of Pharmacology at Strassbourg (1872)

Pioneer studies on autonomic nervous system, nicotine, muscarine

Chloroform blood levels
RUDOLPH BUCHEIM
1820 – 1879

Photo of Rudolph Bucheim
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
*Beitrage zur Arzneimittellehre, 1849*
FOUNDERS OF AMERICAN CLINICAL PHARMACOLOGY

Photos of Harry Gold and Walter Modell
Partial List of GOLD and MODELL Accomplishments

1937 – Introduced Double-Blind Clinical Trial Design\(^1\)

1939 – Initiated \textit{Cornell Conference on Therapy}

1953 – Analyzed Digoxin Effect Kinetics to Estimate Absolute Bioavailability as well as Time-Course of Chronotropic Effects\(^2\)

1960 - Founded \textit{Clinical Pharmacology and Therapeutics}

\(^1\) Gold H, Kwit NT, Otto H. JAMA 1937;108:2173-2179.
LINEAGE of Modern
CLINICAL PHARMACOLOGY

Pater Familias
Rudolph Bucheim

Founding Fathers

US  Europe
Harry Gold  Paul Marini
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 ADR

A SERIOUS ADVERSE DRUG REACTION is 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

Chemical structure of thalidomide
PHOCOMELIA

Photo of an infant with 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

Chart showing lineage of modern clinical pharmacology with Pater Familias and Rudolph Bucheim at the top level followed by the Founding Fathers in the United States, Harry Gold and Walter Modell along side the Founding Father in Europe Paul Martini. Below those names are the names of the Renaissance Leaders in the United States Ken Melmon, John Oates, Leon Goldberg, Dan Azarnoff, Jan Koch-Weser and Lou Lasagna next to the renaissance leaders in Europe Folke Sjoqvist and Collin Dollery.
HISTORY OF CLINICAL PHARMACOLOGY

Albert Sjoerdsma, M.D., Ph.D.

Experimental Therapeutics Branch
National Heart Institute (1958-1971) Lou Gillespie, John Oates,
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

Subjects of Module 5 in our course
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

Chemical structure of Allopurinol

NEW INDICATION:
ALLOPURINOL (Gout) - RW Rundles

ENDOGENOUS COMPOUND:
DOPAMINE (Shock) - LI Goldberg

DRUG METABOLITE:
FEXOFENADINE (Antihistamine) - RL Woosley et al.
DOPAMINE\textsuperscript{1}

Chemical structure of Dopamine

\textsuperscript{1}Goldberg LI. Pharmacol Rev 1972;24:1-29.
MEDICINES “DISCOVERED” BY CLINICAL INVESTIGATORS

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ALLOPURINOL (Gout) - RW Rundles

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FEXOFENADINE (Antihistamine) - RL Woosley et al.
TORSADES DE POINTES

Electrocardiogram of drug-induced arrhythmia.
TERFENADINE METABOLISM\textsuperscript{1}

Chemical structures of Terfenadine and Terfenadine Carboxylate

\textsuperscript{1}From Woosley RL, et al. JAMA 1993;269:1532-6.
PHASES OF PRE-MARKETING DRUG DEVELOPMENT

Chart showing the phases of developing a drug
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)

chart
Thalidomide: Therapeutic Uses

*Erythema Nodosum Leprosum*
Multiple Myeloma

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
Interindividual Variation in Drug Exposure (AUC)

Karim A et al, 2007

Chart showing variability in AUC for pioglitazone and metformin in males and females.

Nortriptyline Drug Exposure
Impact of CY2D6 Polymorphism

Impact of CYP2D6 Polymorphism

Chart showing the impact of CYP2D6 gene duplication

Genetics and Severe Drug Toxicity

HLA-B*5701
Abacavir hypersensitivity
Fluoxacillin 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

Flow chart showing rationale for plasma level monitoring
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

U = URINE CONCENTRATION
V = URINE VOLUME / TIME
P = PLASMA CONCENTRATION
CREATININE CLEARANCE REVISITED

equations
STEADY STATE CONCENTRATION

Continuous Creatinine Synthesis equation

Continuous Drug Infusion equation
COCKCROFT & GAULT EQUATION*

Equation

COCKCROFT & GAULT EQUATION

Equation
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*

Shows a chart illustrating that impaired renal function increases risk of digoxin toxicity.

ESTIMATED $\text{Cl}_\text{Cr}$

*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*

Pie-chart showing that

- 33% are due to renal impairment
- 42% are due to advanced age
- 19% are due to patient weight
- And 6% are due to other factors

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