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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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

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

Daniel McAnally
Benita Bazemore
Recommended Text


Photo of Book Cover
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

Photos of Harry Gold and 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

PROFESSIONAL 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
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
Fluvoxacinill liver injury (DILI)

HLA-B*1502
Carbamazepine-induced
Stevens-Johnson syndrome
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).
TORSADES DE POINTES

Electrocardiogram of drug-induced arrhythmia.
TERFENADINE METABOLISM

Chemical structures of Terfenadine and Terfenadine Carboxylate

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
Development and Evaluation of New Drugs

Drug discovery

Pre-clinical and clinical evaluation

Subjects of Module 5 in our course
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.)*
Pharmacokinetics (PK)

Introduction

Clinical Pharmacokinetics
PHARMACOKINETICS

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

ABSORPTION,
DISTRIBUTION,
METABOLISM, and
EXCRETION
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
“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.
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

\[ U = \text{URINE CONCENTRATION} \]
\[ V = \text{URINE VOLUME / TIME} \]
\[ P = \text{PLASMA CONCENTRATION} \]
CREATININE CLEARANCE REVISITED

equations
STEADY STATE CONCENTRATION

Continuous Creatinine Synthesis equation

Continuous Drug Infusion equation
COCKCROFT & GAULT EQUATION*

Equation

COCKCROFT & GAULT EQUATION

Equation
RENAL FUNCTION IN PATIENTS TOXIC FROM DIGOXIN*

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

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
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

Europe
Paul Marini
LINEAGE OF Modern Clinical Pharmacology

Chart showing lineage of modern clinical pharmacology with Pater Familias and Rudolph Buchheim 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