Principles of Clinical Pharmacology
Remote Sites 2009 - 2010

Cincinnati’s Children’s Hospital Medical Center
Duke University Medical Center, Durham
University of California, Los Angeles
Harbor-UCLA Medical Center, Los Angeles
Hoffman-La Roche, Inc., Nutley, NJ
Indiana University-Purdue University, Indianapolis
Howard University, Washington DC
Principles of Clinical Pharmacology
Remote Sites 2009-2010

Case Western Reserve University, Cleveland, OH
Johnson & Johnson, Titusville, NJ
Johnson & Johnson, San Diego, CA
Johnson & Johnson, Wayne, PA
University of Pennsylvania, Philadelphia
Walter Reed Army Institute of Research and
USUHS, Silver Spring, Maryland
Principles of Clinical Pharmacology
International Remote Sites 2009-2010

Dong-A Medical College
Busan, South Korea
Inha University Hospital
Incheon, South Korea
Instituto Nacional de Enfermedades eoplasicas (INEN), Lima, Peru
Hospital Nacional Arzobispo Loayza, Lima, Peru
Principles of Clinical Pharmacology
Remote Sites 2009-2010

NCI - Frederick, Maryland
NIA - Baltimore, Maryland
NIDA - Baltimore, Maryland
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 IN HUMANS
CAREER GOALS OF CLINICAL PHARMACOLOGISTS

Optimize understanding and use of existing medicines

Discover, develop and evaluate new medicines

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 19th and 20th centuries.
JOHN JACOB ABEL
1857 – 1938

Photo of John Jacob Abel in a laboratory.
OSWALD SCHMIEDEBERG
1838 – 1921

Photo of Oswald Schmiedeberg
RUDOLPH BUCHEIM
1820 – 1879

Photo of Rudolph Bucheim
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 Buchheim

*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
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

LINEAGE of Modern
CLINICAL PHARMACOLOGY

Pater Familias
Rudolph Bucheim

Founding Fathers

<table>
<thead>
<tr>
<th>US</th>
<th>Europe</th>
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</thead>
<tbody>
<tr>
<td>Harry Gold</td>
<td>Paul Marini</td>
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Drug Toxicity
Adverse Drug Reactions

We need to develop drugs that are both effective and safe for use in patients.

While some toxicities can be managed and may be acceptable (risk/benefit ratio) others are by their nature and severity unacceptable.

Covered in Modules 2 and 4 in our course.
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.
THALIDOMIDE

Chemical structure of thalidomide
PHOCOMELIA

Photo of an infant with phocomelia.
Drug Exposure “in utero”

The problem of
“Drug Therapy in Pregnant and Nursing Women”

Covered in Module 4 in our course.
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.)*

Used with *extreme caution* in females of childbearing potential. Contraceptive measures are mandatory.
A recent 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 recent 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 recent example – Cytokine storm (3)

Preclinical models did not predict the risk of this reaction!

Problem of simultaneous dosing in 6 volunteers (first-in-human dosing)

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.
FACTORS CONTRIBUTING TO ADR’S

1. Inappropriate polypharmacy resulting in adverse drug interactions
2. Lack of clear therapeutic goals
3. Failure to attribute new symptoms or abnormal laboratory test results to drugs prescribed
4. Low priority given to studying ADR’s
5. Insufficient knowledge of pharmacology
ADVERSE DRUG REACTIONS

**WHO:**
*Any* untoward reaction to a drug

**CONTEMPORARY VIEW:**
*Unpredictable* Adverse Drug Events
ADVERSE DRUG EVENTS*

Drawing of overlapping circles showing adverse drug events.
CHARACTERISTICS OF MOST ADRs\textsuperscript{1}

MOST \textit{\textbf{\text{NOT}} CAUSED BY NEW DRUGS}

MOST \textit{\textbf{\text{NOT}} IDIOSYNCRATIC}
REACTIONS

\~80\% \textit{\textbf{\text{ARE}} RELATED TO DRUG DOSE}

“Target concentration” strategy

Based on observed *individual variation in drug exposure (AUC)* when “standard” doses are prescribed.

Attempts to “*individualize*” *therapy* when therapeutic and toxic ranges of drug concentrations in plasma have been established.
RATIONALE FOR PLASMA LEVEL MONITORING

Flow chart showing rationale for plasma level monitoring
NONCANCER DRUGS CAUSING ADR’S*

PHENYTOIN**  CARBAMAZEPINE**
PREDNISONE  CODEINE
DIGOXIN**  LITHIUM**
AMIODARONE  THEOPHYLLINE**
ASPIRIN**  DESIPRAMINE**
CO-TRIMOXAZOLE  DEXAMETHASONE
PENTAMIDINE  GENTAMICIN**

* 1988 NMH Data (Clin Pharmacol Ther 1996;60:363-7)
** DRUGS FOR WHICH PLASMA LEVELS ARE AVAILABLE
INCIDENCE OF ADRs*

IN HOSPITALIZED PATIENTS
   All severities 10.9 %
   Serious 2.1 %
   Fatal 0.2 %

AS CAUSE OF HOSPITAL ADMISSION
   Serious 4.7 %
   Fatal 0.13 %

ATTENTION FOCUSED ON MEDICAL ERRORS

“TO ERR IS HUMAN: BUILDING A SAFER HEALTH SYSTEM”

Committee on Quality of Health Care in America
Institute of Medicine

Development and Evaluation of New Drugs

Drug discovery

Pre-clinical and clinical evaluation

Subjects of *Module 5* in our course
NEW INDICATION:
ALLOPURINOL (Gout) - RW Rundles

ENDOGENOUS COMPOUND:
DOPAMINE (Shock) - LI Goldberg

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

Chemical structure of Allopurinol

\textsuperscript{1} Rundles RW, Metz EN, Silberman HR. Ann Intern Med 1966;64:229-57.
MEDICINES “DISCOVERED” BY CLINICAL INVESTIGATORS

NEW INDICATION:
  ALLOPURINOL (Gout) - RW Rundles

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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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TORSADES DE POINTES

Electrocardiogram of drug-induced arrhythmia.
TERFENADINE METABOLISM

Chemical structures of Terfenadine and Terfenadine Carboxylate

DRUG DEVELOPMENT COST PER APPROVED DRUG*

Chart showing that clinical costs of drug development amount to 56%-68% of total costs.

PHASES OF PRE-MARKETING DRUG DEVELOPMENT

Chart
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.

Cytochrome P450 2D6

Absent in 7% of Caucasians
Hyperactive in up to 30% of East Africans
Catalyzes primary metabolism of:
  - propafenone
  - codeine
  - β-blockers
  - tricyclic antidepressants
  - tamoxifene
  - Inhibited by: quinidine, paroxetine, sertraline, venlafaxine
Nortriptyline Drug Exposure
Impact of CYP2D6 Polymorphism

Chart showing the impact of CYP2D6 gene duplication

CYP2D6 and Endoxifen Concentrations

Courtesy of Dr. David Flockhart

Chart showing the plasma Endoxifen (nM) over Wt/Wt, no inhibitor, Venlafaxine, Sertraline, Paroxetine, and *4/*4, no inhibitor. *4/*4, no inhibitor has the lowest plasma Endoxifen (nM).

Genetics and Severe Drug Toxicity

**HLA-B*5701**
Abacavir hypersensitivity
Flucloxacillin 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
PHARMACOKINETICS

Because it is quantitative, pharmacokinetics is of necessity mathematical
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
CREATININE CLEARANCE REVISITED

equations
STEADY STATE CONCENTRATION

equations
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.

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.