Principles of Clinical Pharmacology
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National Institutes of Health
Clinical Center

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Principles of Clinical Pharmacology
Remote Sites 2010 - 2011
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
Cummings School of Veterinary Medicine
    at Tufts University, North Grafton
Wayne State University, Detroit
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University of Pennsylvania, Philadelphia
University of North Carolina, Chapel Hill
Walter Reed Army Institute of Research and
USUHS, Silver Spring, Maryland
University of Iowa, Iowa City
Eli Lilly and Company, Indianapolis
Johnson & Johnson, San Diego
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JSS University,
Mysore, India
University of Sao Paolo,
San Paolo, Brazil
National Academy of Medicine,
Buenos Aires, Argentina
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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
Erasmus University Medical Center
Rotterdam, The Netherlands
Principles of Clinical Pharmacology
Remote Sites 2010-2011

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
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
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.
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
(vividialysis 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 Buchheim

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 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 ¹
1939 – Initiated Cornell Conference on Therapy
1953 – Analized Digoxin Effect Kinetics to Estimate Absolute Bioavailability as well as Time-Course of Chronotropic Effects²
1960 - Founded Clinical Pharmacology and Therapeutics

LINEAGE of Modern
CLINICAL PHARMACOLOGY

Pater Familias
Rudolph Bucheim

Founding Fathers

US                  Europe
Harry Gold          Paul Marini
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 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

Serotonin, carcinoid syndrome, antidepressant drugs
Pheochromocytoma, antihypertensive drugs
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

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 “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**

<table>
<thead>
<tr>
<th>Drug 1</th>
<th>Drug 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>PHENYTOIN**</td>
<td>CARBAMAZEPINE**</td>
</tr>
<tr>
<td>PREDNISONE</td>
<td>CODEINE</td>
</tr>
<tr>
<td>DIGOXIN**</td>
<td>LITHIUM**</td>
</tr>
<tr>
<td>AMIODARONE</td>
<td>THEOPHYLLINE**</td>
</tr>
<tr>
<td>ASPIRIN**</td>
<td>DESIPRAMINE**</td>
</tr>
<tr>
<td>CO-TRIMOXAZOLE</td>
<td>DEXAMETHASONE</td>
</tr>
<tr>
<td>PENTAMIDINE</td>
<td>GENTAMICIN**</td>
</tr>
</tbody>
</table>

* 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
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\textsuperscript{1}

Chemical structure of Allopurinol

\textsuperscript{1} Rundles RW, Metz EN, Silberman HR. Ann Intern Med 1966;64:229-57.
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DOPAMINE\textsuperscript{1}

Chemical structure of Dopamine

\textsuperscript{1}Goldberg LI. Pharmacol Rev 1972;24:1-29.
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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 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.
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
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
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

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 Cl\textsubscript{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.