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

Principles of Clinical Pharmacology

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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International Sites 2011-2012

CIDEIM
Cali, Colombia
Fundacion Valle del Lili
Cali, Colombia

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International Sites 2011-2012

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 Coordinator
301-435-6618
baileyla@mail.nih.gov

Avril Bertrand
Benita Bazemore

PCP Course Team

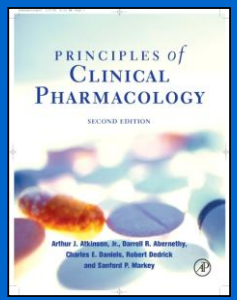
Our Colleagues at:

- 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



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 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

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

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

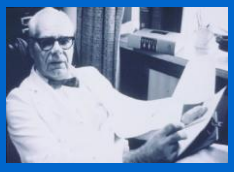
"Fortunately a surgeon who uses the wrong side of the scalpel cuts his own fingers and not the patient; if the same applied to drugs they would have been investigated very carefully a long time ago."

Placing emphasis on therapeutic technique and rational prescribing

Rudolph Bucheim
Beitrage 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*

* Gold H, Kwit NT, Otto H. JAMA 1937;108:2173-2179.
† Gold H, Cattell McK, Greiner T, Hanlon LW, Kwit NT, Modell W, Cotlove E, Benton J, Otto HL. J Pharmacol Exp Ther 1953:109;45-57.

LINEAGE of Modern Clinical Pharmacology

PATER FAMILIAS

RUDOLPH BUCHEIM

FOUNDING FATHERS

US	EUROPE
HARRY GOLD	PAUL MARTINI
WALTER MODELL	

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*

* Melmon KL. N Engl J Med 1971;284:1361-8.

"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

***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.

N Engl J Med 2006;355:1018-1028

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."

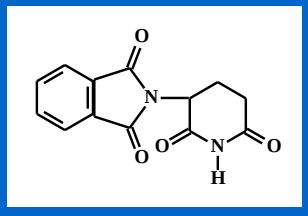
N Engl J Med 2006;355:1018-1028

A modern example – Cytokine storm (3)

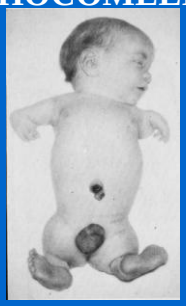
Preclinical models *did not predict the risk* of this reaction!

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

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RUDOLPH BUCHEIM

FOUNDING FATHERS

US	EUROPE
HARRY GOLD WALTER MODELL	PAUL MARTINI

RENAISSANCE LEADERS

US		EUROPE
KEN MELMON LEON GOLDBERG	JOHN OATES DAN AZARNOFF	FOLKE SJÖQVIST

HISTORY OF CLINICAL PHARMACOLOGY

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*

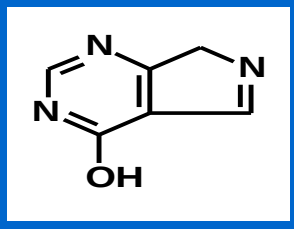
***ENDOGENOUS COMPOUND*:**

DOPAMINE (Shock) - *LI Goldberg*

***DRUG METABOLITE*:**

FEXOFENADINE (Antihistamine) - *RL Woosley at al.*

ALLOPURINOL*



* Rundles RW, Metz EN, Silberman HR. Ann Intern Med 1966;64:229-57.

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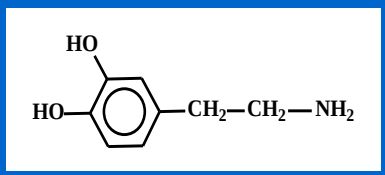
DOPAMINE*



*Goldberg LI. Pharmacol Rev 1972;24:1-29.

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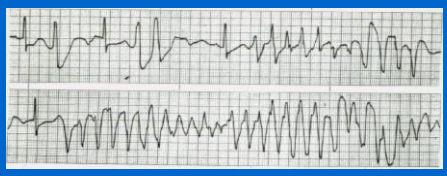
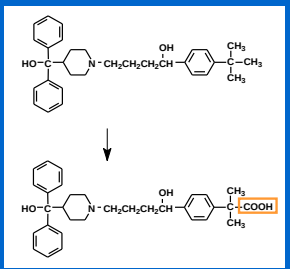
TORSADES DE POINTES



TERFENADINE METABOLISM*

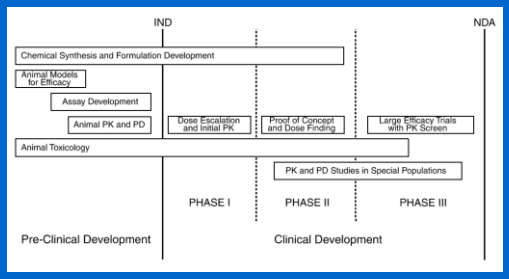


TERFENADINE (SELDANE)

TERFENADINE CARBOXYLATE (ALLEGRA)

*** From Woosley RL, et al. JAMA 1993;269:1532-6.**

PHASES OF PRE-MARKETING DRUG DEVELOPMENT



Phases of Drug Development

"Learn and Confirm" Paradigm

Phase I and II: **The learning phases.**

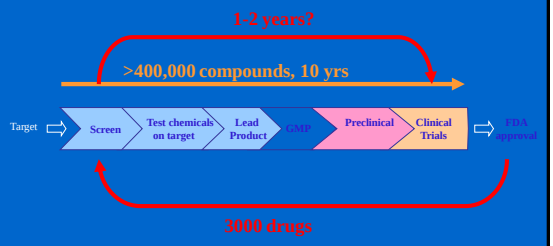
Phase III: **The confirmatory phase.**

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)



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

Interindividual Variation in Drug Exposure (AUC)

Karim A et al, 2007

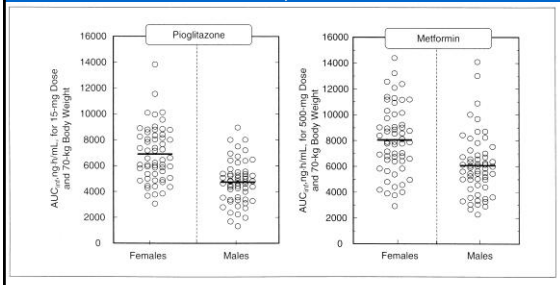
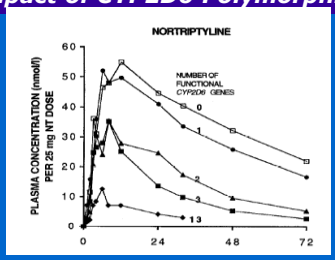


Figure 3. Body weight- and dose-adjusted arithmetic mean (—) and individual values for pioglitazone (left panel) and metformin (right panel) AUC, in females and males following single oral doses of commercial pioglitazone (15 mg) and metformin (500 mg or 850 mg) tablets given together to young healthy subjects.

44 • J Clin Pharmacol 2007;47:37-47

Nortriptyline Drug Exposure
Impact of CYP2D6 Polymorphism



Dalen P *et al. Clin Pharmacol Ther* 1998;63:444-452

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

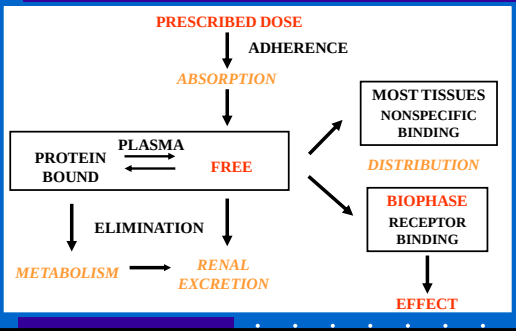
- This will be the subject of *Module 1* in our course.
- *Essential* for integration of material in subsequent course modules.

PHARMACOKINETICS

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

ABSORPTION,
DISTRIBUTION,
METABOLISM, and
EXCRETION

RATIONALE FOR PLASMA LEVEL MONITORING



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*

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

[reduce estimate by 15% for women]

*** Cockroft DW, Gault MH: Nephron 1976;16:31-41.**

COCKCROFT & GAULT EQUATION

$$CL_{Cr} = \frac{I}{P}$$

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

[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**

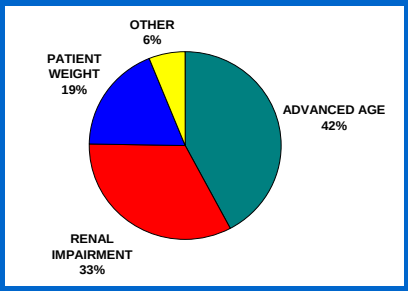
SERUM Cr (mg %)	Cl_{Cr} (mL/min) ≥ 50	< 50	
≤ 1.7	4	19	52%
> 1.7	0	21	48%

* From Piergies AA, et al. Clin Pharmacol Ther 1994;55:353-8.

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.