

Principles of Clinical Pharmacology

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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

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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

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International Remote Sites 2009-2010

Dong-A Medical College

Busan, South Korea

Inha University Hospital

Incheon, South Korea

**Instituto Nacional de Enfermedades eoplasticas (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

Pharmacology, Second Edition by Arthur J. Atkinson, Jr., et al,
published by Academic Press

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 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 Design¹

1939 – Initiated *Cornell Conference on Therapy*

1953 – Analyzed Digoxin Effect Kinetics to Estimate Absolute Bioavailability as well as Time-Course of Chronotropic Effects²

1960 - Founded *Clinical Pharmacology and Therapeutics*

¹ *Gold H, Kwit NT, Otto H. JAMA 1937;108:2173-2179.*

² *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

<u>US</u>	<u>Europe</u>
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.

***N Engl J Med* 2006;355:1018-1028**

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.”

N Engl J Med 2006;355:1018-1028

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)**

Copy of the top of a page from the New England Journal of Medicine of a Brief Report showing the title of an article entitled Cytokine Storm in a Phase I Trial of the Anti-CD28 Monoclonal Antibody TGNI412, by G Suntharalingam, F.R.C.A, et al.

N Engl J Med 2006;355:1018-28

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 ADRs¹

MOST NOT CAUSED BY NEW DRUGS

**MOST NOT IDIOSYNCRATIC
REACTIONS**

~ 80% ARE RELATED TO DRUG DOSE

¹ Melmon KL. N Engl J Med 1971;284:1361-8.

“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**

PREDNISONE

DIGOXIN**

AMIODARONE

ASPIRIN**

CO-TRIMOXAZOLE

PENTAMIDINE

CARBAMAZEPINE**

CODEINE

LITHIUM**

THEOPHYLLINE**

DESIPRAMINE**

DEXAMETHASONE

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 %

Lazarou J, et al. JAMA 1998;279:1200-05.

**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**

<http://www.nap.edu/reading room> (2000).

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 et al.*

ALLOPURINOL¹

Chemical structure of Allopurinol

¹ Rundles RW, Metz EN, Silberman HR. *Ann Intern Med* 1966;64:229-57.

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*RL Woosley et al.***

DOPAMINE¹

Chemical structure of Dopamine

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

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*RL Woosley et al.***

TORSADES DE POINTES

Electrocardiogram of drug-induced arrhythmia.

TERFENADINE METABOLISM¹

Chemical structures of Terfenadine and Terfenadine Carboxylate

¹From Woosley RL, et al. JAMA 1993;269:1532-6.

DRUG DEVELOPMENT COST PER APPROVED DRUG*

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

*** DiMasi JA, et al. J Health Econ 2003;22:151-85.**

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.

J Clin Pharmacol 2007;47:37-47

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

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

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).

Jin Y et al: J Natl Cancer Inst 97:30, 2005

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

equations

COCKCROFT & GAULT EQUATION*

Equation

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

COCKCROFT & GAULT EQUATION

Equation

***RENAL FUNCTION IN PATIENTS
TOXIC FROM DIGOXIN****

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

*** 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*

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.**