Principles of Clinical Pharmacology

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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

Principles of Clinical Pharmacology

Remote Sites 2010-2011

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

Principles of Clinical Pharmacology

International Sites 2010-2011

JSS University,
Mysore, India
University of Sao Paolo,
San Paolo, Brazil
National Academy of Medicine,
Buenos Aires, Argentina

Principles of Clinical Pharmacology

International Sites 2010-2011

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

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

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.

JOHN JACOB ABEL
1857 – 1938

Photo of John Jacob Abel in a laboratory.

John Jacob Abel

“Father of American Pharmacology”

First fulll-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 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

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 Effects[2]
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

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.

***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 Monocolonal 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.

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

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

<u>WHO</u>:
***Any* untoward reaction to a drug**

<u>CONTEMPORARY VIEW</u>:
***Unpredictable* Adverse Drug Events**

ADVERSE DRUG EVENTS*

Drawing of overlapping circles showing adverse drug events.

CHARACTERISTICS OF MOST ADRs[1]

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**	**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 %

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 at al*.

ALLOPURINOL[1]

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.

DOPAMINE[1]

Chemical structure of Dopamine

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

MEDICINES "DISCOVERED" BY CLINICAL INVESTIGATORS

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RL Woosley et al.

TORSADES DE POINTES

Electrocardiogram of drug-induced arrhythmia.

TERFENADINE METABOLISM[1]

Chemical structures of Terfenadine and Terfenadine Carboxylate

[1]From 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 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.

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

Continuous Creatinine Synthesis equation

Continuous Drug Infusion equation

COCKCROFT & GAULT EQUATION*

Equation

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

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.

*** 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.**