Principles of Clinical Pharmacology

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Principles of Clinical Pharmacology

Remote Sites 2008-2009

Darmouth Hitchcock Medical Center, Lebanon
Dong-A Medical College, Republic of Korea
Duke University Medical Center, Durham
Harbor-UCLA Medical Center, Los Angeles
Indiana University-Purdue University, Indianapolis
University of California, Los Angeles
University of California, San Francisco
University of Pennsylvania, Philadelphia
University of Puerto Rico, San Juan
Walter Reed Army Institute of Research – USUHS, Silver Spring, Maryland

Principles of Clinical Pharmacology

Remote Sites 2008-2009

NCI - Frederick, Maryland
NIA - Baltimore, Maryland
NIA – Harbor Hospital, Baltimore, MD
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

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

Photo of Book Cover

Certificate awarded to a student for attending 75% of the 31 lectures in the course.

PHARMACOLOGY

The study of *drugs* (chemicals, “small molecules”) and *biologics* (peptides, antibodies, “large molecules”) and their actions in *living organisms* (intact animals, isolated organs, tissue cultures).

CLINICAL PHARMACOLOGY

The Study of Drugs in Humans

COURSE FOCUS

- Scientific basis of drug use,
  Development and evaluation
- NOT Therapeutics
- Emphasis is on General Principles
  For both “old” and “new” drugs

CAREER GOALS OF CLINICAL PHARMACOLOGISTS

Optimize understanding and use of existing medicines

Develop and evaluate new medicines

“Introduction” Lecture Outline

- **Historical overview**
- **The problem of adverse drug reactions (ADRs)**
- **Drug discovery and development**
- **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 Oswarld 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 *LINEAGE* of Modern

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

The top chart shows Pater Familias' name followed by Rudolph Bucheim's name beneath Pater Familias' name. Beneath their names are the names of the Founding Fathers, Harry Gold and Walter Modell in the United States and Paul Martini in Europe.

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.**

THALIDOMIDE

Chemical formula for 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.

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.

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 Stated 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

A recent example – Cytokine Storm

"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.

***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**

Preclinical models did not predict the risk of this reaction!

Picture of “Brief report entitled Cytokine Storm in a Phase 1 Trial of the Anti-CD28 Monoclonal Antibody TGM1412

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**

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**

A list of these drugs

Interindividual Variation in Drug Exposure (AUC) Karim A et al, 2007

Slide showing this

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*

Chemical structure

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DOPAMINE*

Chemical structure of dopamine

TORSADES DE POINTES

Chart

TERFENADINE METABOLISM*

Chemical structure of Terfenadine and Terfenadine Carboxylate

DRUG DEVELOPMENT COST PER APPROVED DRUG*

Chart showing this.

PHASES OF PRE-MARKETING DRUG DEVELOPMENT

Chart

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*

Shows equation

COCKCROFT & GAULT EQUATION

Shows equation

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

Contains a chart reflecting this

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