Principles of Clinical Pharmacology

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Clinical Pharmacology Program

Office of Clinical Research Training
and Medical Education
National Institutes of Health
Clinical Center
September 2, 2010
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 and Johnson, San Diego
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International Sites 2010-2011

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

PRINCIPLES OF CLINICAL PHARMACOLOGY
SECOND EDITION

Arthur J. Atkinson, Jr., Darrell R. Abernethy,
Charles E. Daniels, Robert Bedrick
and Sanford P. Markey
PHARMACOLOGY

The study of drugs and biologics and their actions in living organisms

Drugs: “small molecules”, chemicals

Biologics: “large molecules”, peptides, antibodies
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
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 therapeutical 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

LINEAGE of Modern Clinical Pharmacology

PATER FAMILIAS
RUDOLPH BUCHEIM

FOUNDING FATHERS
US
HARRY GOLD
WALTER MODELL

EUROPE
PAUL MARTINI
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.
A SERIOUS ADVERSE DRUG REACTION is an adverse drug reaction (ADR) that requires or prolongs hospitalization, is permanently disabling or results in death.
THALIDOMIDE
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)
Cytokine Storm in a Phase 1 Trial of the Anti-CD28 Monoclonal Antibody TGN1412

Ganesh Suntharalingam, F.R.C.A., Meghan R. Perry, M.R.C.P.,
Stephen Ward, F.R.C.A., Stephen J. Brett, M.D., Andrew Castello-Cortes, F.R.C.A.,
Michael D. Brunner, F.R.C.A., and Nicki Panoskaltsis, M.D., Ph.D.

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

PATER FAMILIAS
RUDOLPH BUCHEIM

FOUNDING FATHERS
US
HARRY GOLD
WALTER MODELL

EUROPE
PAUL MARTINI

RENAISSANCE LEADERS

US
KEN MELMON
LEON GOLDBERG

JOHN OATES
DAN AZARNOFF

EUROPE
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
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*

Medication Errors

Adverse Drug Events (ME & ADR)

- **MEDICATION ERROR:** preventable ADE plus near misses
- **ADVERSE DRUG EVENT:** preventable & unpredictable events with harm to the patient
- **ADVERSE DRUG REACTION:** generally unpredictable ADE

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.
RATIONAL FOR PLASMA LEVEL MONITORING

PRESCRIBED DOSE

ADHERENCE

ABSORPTION

PROTEIN BOUND PLASMA FREE

DISTRIBUTION

MOST TISSUES NONSPECIFIC BINDING

METABOLISM

ELIMINATION

RENAL EXCRETION

BIOPHASE RECEPTOR BINDING

EFFECT
# Noncancer Drugs Causing ADR’s*

<table>
<thead>
<tr>
<th>Drug</th>
<th>Drug</th>
</tr>
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<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*

MEDICINES “DISCOVERED” BY CLINICAL INVESTIGATORS

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DOPAMINE*

MEDICINES “DISCOVERED” BY CLINICAL INVESTIGATORS

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ENDOGENOUS COMPOUND:
  DOPAMINE (Shock) - LI Goldberg

DRUG METABOLITE:
  FEXOFENADINE (Antihistamine) - RL Woosley et al.
TORSADES DE POINTES
TERFENADINE METABOLISM

<table>
<thead>
<tr>
<th></th>
<th>COST ($ x 10^6)†</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OUT-OF-POCKET</td>
<td>CAPITALIZED</td>
<td></td>
</tr>
<tr>
<td>TOTAL COSTS</td>
<td>403</td>
<td>802</td>
<td></td>
</tr>
<tr>
<td>CLINICAL COSTS</td>
<td>274 (68%)</td>
<td>453 (56%)</td>
<td></td>
</tr>
</tbody>
</table>

† BASED ON 21.5% SUCCESS RATE

PHASES OF PRE-MARKETING DRUG DEVELOPMENT

IND
- Chemical Synthesis and Formulation Development
- Animal Models for Efficacy
  - Assay Development
  - Animal PK and PD
- Animal Toxicology

Pre-Clinical Development

PHASE I
- PK and PD Studies in Special Populations

PHASE II
- Proof of Concept and Dose Finding

PHASE III
- Large Efficacy Trials with PK Screen

Clinical Development

NDA
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.
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.
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
  - tamoxifen
  - Inhibited by: quinidine, paroxetine, sertraline, venlafaxine
Nortriptyline Drug Exposure
Impact of CYP2D6 Polymorphism

CYP2D6 and Endoxifen Concentrations

Courtesy of Dr. David Flockhart

Plasma Endoxifen (nM)

Wt/Wt, no inhibitor
Venlafaxine
Sertraline
Paroxetine
*4/*4, no inhibitor

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
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

\[ \text{CL}_{\text{Cr}} = \frac{U \times V}{P} \]

- **U** = URINE CONCENTRATION
- **V** = URINE VOLUME / TIME
- **P** = PLASMA CONCENTRATION
CREATININE CLEARANCE REVISITED

RATE OF APPEARANCE OF Cr IN URINE (dE/dt):
\[ \frac{dE}{dt} = \text{CL}_{\text{Cr}} \times P \]

RATE OF CHANGE OF Cr IN BODY (dX/dt):
\[ \frac{dX}{dt} = I - \text{CL}_{\text{Cr}} \times P \]

AT STEADY STATE:
\[ P = \frac{I}{\text{CL}_{\text{Cr}}} \]

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*

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

[reduce estimate by 15% for women]

COCKCROFT & GAULT EQUATION

\[ CL_{Cr} = \frac{I}{P} \]

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

[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
<table>
<thead>
<tr>
<th>SERUM Cr (mg %)</th>
<th>Cl\textsubscript{Cr} (mL/min)</th>
<th>\geq 50</th>
<th>&lt; 50</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>\leq 1.7</td>
<td>4</td>
<td>19</td>
<td></td>
<td>52%</td>
</tr>
<tr>
<td>&gt; 1.7</td>
<td>0</td>
<td>21</td>
<td></td>
<td>48%</td>
</tr>
</tbody>
</table>

ESTIMATED $\text{Cl}_{\text{Cr}}$

- **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.