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
September 3, 2009

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

Principles of Clinical Pharmacology
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, PA
Walter Reed Army Institute of Research and USUHS, Silver Spring, Maryland
Principles of Clinical Pharmacology
International Remote Sites 2009-2010

Dong-A Medical College
Busan, South Korea
Inha University Hospital
Incheon, South Korea
Instituto Nacional de Enfermedades Neoplasicas (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
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

**OSWALD SCHMIEDEBERG**  
1838 - 1921
RUDOLPH BUCHEIM
1820 - 1879

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 Arzneimitteltechnik, 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 BUCHHEIM

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.
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](image)

PHOCOMELIA

![Image of a baby with phocomelia](image)
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)
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 FAMILIAS
US
HARRY GOLD
WALTER MODELL
EUROPE
PAUL MARTINI

RENAISSANCE LEADERS
US
KEN MELMON
JAN KOCH-WESER
JOHN OATES
LOE LASAGNA
EUROPE
FOLKE SJÖQVIST
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*

• MEDICATION ERROR: preventable ADE plus near misses
• ADR EVENT: preventable & unpredictable events with harm to the patient
• ADR 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.

**RATIONALE FOR PLASMA LEVEL MONITORING**

**PRESCRIBED DOSE** → **ADHERENCE** → **ABSORPTION** → **PROTEIN BOUND** \(\leftrightarrow\) **PLASMA FREE** → **ELIMINATION** → **METABOLISM** \(\downarrow\) **RENAL EXCRETION** → **EFFECT** → **RECEPTOR BINDING** → **BIOPHASE BINDING** → **MOST TISSUES NONSPECIFIC BINDING**

**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 %


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 Randles

ENDOGENOUS COMPOUND:
DOPAMINE (Shock) - LI Goldberg

DRUG METABOLITE:
FEXOFENADINE (Antihistamine) - RL Woosley et al.

ALLOPURINOL*  
DOPAMINE

HO
HO
\[\text{CH}_2-\text{CH}_2-\text{NH}_2\]


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.

TORSADES DE POINTES
**TERFENADINE METABOLISM**


**DRUG DEVELOPMENT COST PER APPROVED DRUG**

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

† BASED ON 21.5% SUCCESS RATE


**PHASES OF PRE-MARKETING DRUG DEVELOPMENT**
Variability in Drug Response

- Pharmacokinetic (PK) basis
- Pharmacodynamic (PD) basis

Both PK and PD variability may be due to **genetic** and/or **environmental** factors.

### 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

---

**Interindividual Variation in Drug Exposure (AUC)**

Karim A et al, 2007

![Graph showing interindividual variation in drug exposure (AUC)]
Nortriptyline Drug Exposure
Impact of CYP2D6 Polymorphism


CYP2D6 and Endoxifen Concentrations

Genetics and Severe Drug Toxicity

HLA-B*5701
Abacavir hypersensitivity
Fluoxacillin 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

\[
CL_{Cr} = \frac{U \times V}{P}
\]

- \( U \) = URINE CONCENTRATION
- \( V \) = URINE VOLUME / TIME
- \( P \) = PLASMA CONCENTRATION
CREATININE CLEARANCE
REVISITED

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

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

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

\[I = \text{RATE OF CREATININE SYNTHESIS}\]

STEADY STATE CONCENTRATION

CONTINUOUS CREATININE SYNTHESIS:
\[
C_{SS} = \frac{I}{\text{CL}_{Cr}}
\]

CONTINUOUS DRUG INFUSION:
\[
C_{SS} = \frac{I}{\text{CL}_{E}}
\]

COCKCROFT & GAULT EQUATION*

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

[reduce estimate by 15% for women]

COCKCROFT & GAULT EQUATION

\[
\text{CL}_{\text{Cr}} = \frac{1}{P}
\]

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

[reduce estimate by 15% for women]

Terms in red estimate creatinine synthesis rate.

RENAL FUNCTION IN PATIENTS TOXIC FROM DIGOXIN*

<table>
<thead>
<tr>
<th>SERUM Cr (mg %)</th>
<th>Cl_{\text{Cr}} (mL/min)</th>
<th>≥ 50</th>
<th>&lt; 50</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 1.7</td>
<td>4</td>
<td>19</td>
<td>52%</td>
</tr>
<tr>
<td>&gt; 1.7</td>
<td>0</td>
<td>21</td>
<td>48%</td>
</tr>
</tbody>
</table>


ESTIMATED 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.