Principles of Clinical Pharmacology
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COURSE FOCUS

Scientific basis of drug use, development and evaluation

*Not* Therapeutics

Emphasis is on *General Principles* for both “old” and “new” drugs
Recommended Text


Photo of Book Cover
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CLINICAL PHARMACOLOGY

Overview and General Scope
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 AND BIOLOGICS IN HUMANS
Translational Sciences

Knowledge acquired in animal or in silico models of disease, ex-vivo studies in human tissues, or in vivo studies in healthy or diseased humans is translated into effective treatment for patients.

Clinical Pharmacology is a translational discipline essential for rational drug development and therapeutics in humans.
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

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

PROFESSIONAL GOALS OF CLINICAL PHARMACOLOGISTS

Discover, develop and evaluate new medicines

Optimize the use of existing medicines, find new indications

Define the basis for variability in therapeutic and toxic responses to medicines
Interindividual Variation in Drug Exposure (AUC)

Karim A et al, 2007

Chart showing variability in AUC for pioglitazone and metformin in males and females.

Nortriptyline Drug Exposure
Impact of CY2D6 Polymorphism

Impact of CYP2D6 Polymorphism

Chart showing the impact of CYP2D6 gene duplication

Genetics and Severe Drug Toxicity

HLA-B*5701
Abacavir hypersensitivity
Flucoxacillin liver injury (DILI)

HLA-B*1502
Carbamazepine-induced
Stevens-Johnson syndrome
Adverse Drug Reactions

We need to develop drugs that are both effective and safe.

Some toxicities can be managed and may be acceptable (risk/benefit ratio) while others are by their nature and severity unacceptable.

Risk/benefit is contextual (drug and disease).
TORSADES DE POINTES

Electrocardiogram of drug-induced arrhythmia.
TERFENADINE METABOLISM$^1$

Chemical structures of Terfenadine and Terfenadine Carboxylate

THALIDOMIDE

Chemical structure of thalidomide
Prenatal Drug Exposure:
PHOCOMELIA

Photo of an infant with phocomelia.
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
Development and Evaluation of New Drugs

Drug discovery

Pre-clinical and clinical evaluation

Subjects of Module 5 in our course
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.
Drug Repurposing

Finding new biological targets and *new therapeutic indications* for “old” drugs.

May shorten drug development time.

Known human pharmacokinetics.

Prior human safety data.
Drug Repurposing (C. Austin, NCATS)

chart
Thalidomide: Repurposing

**Erythema Nodosum Leprosum**
Astute clinical observation of benefit

**Multiple Myeloma**
Targeted development

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.)**
Novel FDA-Approved Indications for “Repurposed Drugs”

- *Apomorphine* - Parkinson’s Disease
- *Sildenafil* - Pulmonary Hypertension
- *Taxotere* - Prostate Cancer
- *Lamotrigine* - Bipolar Disorder
- *Bevacizumab* - Lung Cancer (non-SQ, non-SCLC)
- *Hydroxyurea* - Sickle Cell Disease
- *Minoxidil* - Scalp hair re-growth (vertex in men)

Source: Product label (package insert)
Pharmacokinetics (PK)

Introduction

Clinical Pharmacokinetics
PHARMACOKINETICS

The *QUANTITATIVE ANALYSIS* of the *TIME COURSE* of DRUG
  ABSORPTION,
  DISTRIBUTION,
  METABOLISM, and
  EXCRETION
Pharmacokinetics – Pharmacodynamics

Chart
Use of Pharmacokinetics

• Basis for *rational dose selection* in therapeutics
• Development and *evaluation of new drugs*
• Basic studies of *drug distribution* (PET Scan)
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

PK/PD modeling approaches
“Target concentration” strategy

Based on observed *individual variation in drug exposure (AUC)* when using “standard” doses.

Attempts to “individualize” therapy when *therapeutic and toxic ranges* of drug concentrations in plasma have been established.

Optimize efficacy, minimize toxicity.
TARGET CONCENTRATION STRATEGY

ESTIMATE INITIAL DOSE
  TARGET LEVEL
  LOADING DOSE
  MAINTENANCE DOSE

BEGIN THERAPY

ASSESS THERAPY
  PATIENT RESPONSE
  DRUG LEVEL

REFINE DOSE ESTIMATE

ADJUST DOSE
DRUG CANDIDATES FOR TDM

• Low therapeutic index
• No physiologic endpoints or biomarkers to guide dosage
• Pharmacokinetics vary widely between individuals
• Need to monitor adherence?
FIRST DESCRIPTION OF THERAPEUTIC DRUG MONITORING

Article

Wuth O. JAMA 1927;88:2013-17
TARGET CONCENTRATION STRATEGY

ESTIMATE INITIAL DOSE
TARGET LEVEL
LOADING DOSE
MAINTENANCE DOSE
DIGOXIN Levels in *TOXIC* and *NONTOXIC* Patients

* From Smith TW and Haber E. J Clin Invest 1970;49:2377-86
TRADITIONAL Guidelines
for DIGOXIN Levels

THERAPEUTIC RANGE: 0.8 - 1.6 ng/mL

POSSIBLY TOXIC LEVELS: 1.6 - 3.0 ng/mL

PROBABLY TOXIC LEVELS: > 3.0 ng/mL
SURVIVAL as a function of DIGOXIN LEVEL measured after 1 Month Rx*

PROPOSED Range of DIGOXIN LEVELS for OPTIMAL THERAPY in CHF

New Therapeutic Range: 0.5 - 0.9 ng/mL

Benefit results from INHIBITION OF SYMPATHETIC NERVOUS SYSTEM rather than ↑ INOTROPY

Question: Doses of digoxin used in this study should have resulted in higher levels? Study limitation: No digoxin levels done after one month in study (patients seen for 48 months).
TARGET CONCENTRATION STRATEGY

ESTIMATE INITIAL DOSE
TARGET LEVEL
LOADING DOSE
MAINTENANCE DOSE

BASED ON CONCEPT OF DISTRIBUTION VOLUME
DIGOXIN LEVELS after IV Dose

graph
SINGLE COMPARTMENT MODEL

equation
3 DISTRIBUTION VOLUMES

equations
INITIAL DIGITALIZATION

picture
DISTRIBUTION DELAYS ONSET
of DIGOXIN Chronotropic Action*

Graph

* From Gold H, et al. J Pharmacol Exp Ther
1953;109:45-57.
TARGET CONCENTRATION STRATEGY

ESTIMATE INITIAL DOSE
TARGET LEVEL
LOADING DOSE
MAINTENANCE DOSE

BASED ON CONCEPTS OF ELIMINATION
HALF LIFE
AND CLEARANCE
ELIMINATION HALF-LIFE

ELIMINATION HALF-LIFE IS THE TIME REQUIRED FOR THE PLASMA CONCENTRATION (OR TOTAL BODY STORES) OF A DRUG TO FALL TO HALF OF THE CONCENTRATION (OR AMOUNT) PRESENT AT SOME PREVIOUS TIME.
ELIMINATION PARAMETERS

equation

t1/2 = elimination half life
k = elimination rate constant
CLE = elimination clearance
MAINTENANCE DIGOXIN THERAPY

Image
DIGOXIN CUMULATION

.25 x 2/3 = .17
  +.25
  .42 x 2/3 = .28
  +.25
  .53 x 2/3 = .36
  +.25
  .61 x 2/3 = .41
  +.25
  .66 x 2/3 = .44
  +.25
  .69 x 2/3 = .46
  +.25
  .71

DOSE #1

DOSE #2

DOSE #3

DOSE #4

DOSE #5

DOSE #6

DOSE #7
CUMULATION FACTOR

equation

\[ \tau = \text{dose interval} \]
\[ k = \text{elimination rate constant} \]
ELIMINATION RATE CONSTANT

equation
LOADING & MAINTENANCE DOSES

Graph
TIME-COURSE OF DIGOXIN CUMULATION

graph
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

\[ U = \text{URINE CONCENTRATION} \]
\[ V = \frac{\text{URINE VOLUME}}{\text{TIME}} \]
\[ P = \text{PLASMA CONCENTRATION} \]
CREATININE CLEARANCE REVISITED

equations
STEADY STATE CONCENTRATION

Continuous Creatinine Synthesis equation

Continuous Drug Infusion equation
COCKCROFT & GAULT EQUATION*

Equation

COCKCROFT & GAULT EQUATION

Equation
RENAL FUNCTION IN PATIENTS
TOXIC FROM DIGOXIN*

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

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
CKD-EPI Collaboration Equation

- Chronic Kidney Disease (CKD) Epidemiology Collaboration Equation
- More accurate than MDRD equation in estimating GFR (eGFR)
- Less bias if GFR >60 ml/min/1.73 m²
- To be discussed in lecture on PK alterations in renal disease
STEADY STATE CONCENTRATION

Continuous infusion:
equation

Intermittent dosing:
equation
STEADY STATE CONCENTRATION

NOT DETERMINED BY LOADING DOSE

MEAN STEADY STATE
CONCENTRATION
NOT DETERMINED BY Vd

PEAK AND TROUGH ARE AFFECTED BY Vd
Vd AFFECTS PEAK AND TROUGH BUT NOT MEAN LEVELS

Graph
STEADY STATE CONCENTRATION

NOT DETERMINED BY LOADING DOSE

MEAN STEADY STATE CONCENTRATION NOT DETERMINED BY Vd

CHANGES IN MAINTENANCE DOSE RESULT IN DIRECTLY PROPORTIONAL CHANGES IN CSS FOR MOST DRUGS
FOR MOST DRUGS, $C_{ss}$ IS PROPORTIONAL TO DOSE (Dosing Rate)

CONTINUOUS INFUSION:
Equation

INTERMITTENT DOSING:
Equation
SOME DRUGS NOT ELIMINATED BY FIRST ORDER KINETICS

PHENYTOIN (DILANTIN)
ETHYL ALCOHOL
ACETYLSALICYLIC ACID (ASPIRIN)
PHENYTOIN HYDROXYLATION

Image
Graph
PHENYTOIN KINETICS
in Normal Subjects

Graph
PATIENT WHO BECAME TOXIC ON A PHENYTOIN DOSE OF 300 mg/day

graph
BASIS OF APPARENT FIRST-ORDER KINETICS

Equations
PHARMACOKINETICS

• **PRACTICE PROBLEMS AT END OF CHAPTER 2**
  WITH **ANSWERS IN APPENDIX II**

• **EQUATIONS DERIVED IN “PRINCIPLES OF CLINICAL PHARMACOLOGY” TEXTBOOK**
Historical Overview

The establishment of *experimental pharmacology* as a discipline in Europe and the USA in the 19\textsuperscript{th} and 20\textsuperscript{th} centuries.
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

Professor of Pharmacology at Strassbourg (1872)

Pioneer studies on autonomic nervous system, nicotine, muscarine

Chloroform blood levels
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.
LINEAGE of Modern
CLINICAL PHARMACOLOGY

Pater Familias
Rudolph Buchheim

Founding Fathers

US Europe
Harry Gold Paul Marini
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,

Lou Gillespie, John Oates, Leon Goldberg, Richard Crout,
Ken Melmon

Serotonin, carcinoid syndrome, antidepressant drugs

Pheochromocytoma, antihypertensive drugs