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

Pharmacology, Third Edition by Arthur J. Atkinson, Jr., et al, published by Academic Press

Photo of Book Cover

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CLINICAL PHARMACOLOGY

Part I: Overview

- General Scope of the Discipline
- Historical Notes
- Role of Clinical Pharmacologists
- Variability in Drug Response
- Adverse Drug Reactions
- Drug 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 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 [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.

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

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.

J Clin Pharmacol 2007;47:37-47

Nortriptyline Drug Exposure
Impact of CY2D6 Polymorphism

Impact of CYP2D6 Polymorphism

Chart showing the impact of CYP2D6 gene duplication

Dalen P *et al*. *Clin Pharmacol Ther* 1998;63:444-452

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

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

[1]From Woosley RL, et al. JAMA 1993;269:1532-6.

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)

Clinical Pharmacology

Part II: Pharmacokinetics

- Basic Concepts
- Clinical Applications
- Apparent Volume of Distribution
- Clearance
- First-order Kinetics
  - Michaelis-Menten Kinetics

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

First Academic Clinical Drug Analysis Lab

Arthur J. Atkinson, Jr., M.D.

Northwestern Memorial Hospital
Chicago, Illinois

TARGET CONCENTRATION STRATEGY

ESTIMATE INITIAL DOSE
TARGET LEVEL
LOADING DOSE
MAINTENANCE DOSE

DIGOXIN Levels in *TOXIC* and *NONTOXIC* Patients*

graph

* 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*

* Rathore SS, et al. JAMA 2003;289:871-8

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 **DOSE #1**
+.25 **DOSE #2**
.42 x 2/3 = .28
+.25 **DOSE #3**
.53 x 2/3 = .36
+.25 **DOSE #4**
.61 x 2/3 = .41
+.25 **DOSE #5**
.66 x 2/3 = .44
+.25 **DOSE #6**
.69 x 2/3 = .46
+.25 **DOSE #7**
.71

CUMULATION FACTOR

equation

τ = dose interval
k = 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 = URINE CONCENTRATION
V = URINE VOLUME / TIME
P = PLASMA CONCENTRATION

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

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.**

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, Css 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

STEADY STATE EQUATION

FIRST ORDER KINETICS

$$DOSE/\tau = CL_E \bullet \overline{C}_{SS}$$

MICHAELIS-MENTEN KINETICS

$$DOSE/\tau = \left[\frac{V_{max}}{K_m + \overline{C}_{SS}}\right]\overline{C}_{SS}$$

RELATIONSHIP OF PLASMA LEVEL TO PHENYTOIN DOSE*

PHENYTOIN DOSE (mg/day)	PLASMA LEVEL µg/mL
300	10
400	20
500	30

(THERAPEUTIC RANGE: 10 – 20 µg/mL)

* From: Kutt H, McDowell F: J Am Med Assoc 1968;203:969-72.

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 19th and 20th centuries.

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

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 Bucheim

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.