PRINCIPLES OF CLINICAL RESEARCH

NIRALI PRAKASHAN

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Edited By

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ADVANCEMENT OF KNOWLEDGE

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PREFACE

The clinical research industry in India is maturing, after a 40 year long hiatus. India is emerging out of the shadows, so far as new drug development is concerned. The needs of the industry in terms of personnel, training and resources are therefore rising. Clinical research is now a part of the syllabi at a number of courses at both bachelor's and master's levels. Many students are now choosing this as a career, and hence there will be a need for teachers too. There is also an urgent need for a textbook of clinical research for the use of students and professionals alike.

The best option in this milieu, would be a book where the expertise of a number of people is pooled, giving the readers the advantage of learning and experience of people from academics and the industry. The present book is our first step in this direction. In this book we have authors from the pharmaceutical and CRO industry, research institutes and educational institutes. With a multi author book one hopes to have continuity, when authors from the present lot retire, they will be replaced by younger people and hopefully the book will continue to be published for years to come.

When one looks back at clinical research over the last three decades, it is changes that have come about, that strike us the most. There were no CROs, CRAs or co-ordinators to help in clinical trials. Most studies involved only one of two individuals, the sponsor, the Medical Advisor and the investigator. The industry looked on clinical research with an indulgent eye, at times as an unavoidable expenditure. The scenario has changed considerably. The industry realizes the importance of clinical research, and the marketing colleagues don't look at us, to provide favourable data for their promotional material.

The pharmaceutical industry based overseas initially was wary about studies conducted in India. From the sheer volume of work that is flowing in, one feels that their confidence is rising. As more and more studies are initiated in the country, new issues are cropping up. The regulators in India are tackling each issue as it emerges and the industry reacts with either a sense of relief or disappointment. There is still need for more understanding among the different stakeholders in research.

This book will hopefully provide students with the much needed Indian perspective of clinical research. It is hoped that more and more professionals from this field will contribute to future editions to make this book a comprehensive source of information.

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Contributors' Profile...

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M.D.

Dr. Apte has done her MBBS and MD (Pharmacology) from Seth GS Medical College and KEM hospital, Mumbai. She has about 6 years experience including teaching experience in GS Medical College, BJ Medical College and Sinhgad Medical College, Pune. She is currently working as a Medical Advisor with Emcure Pharmaceuticals Ltd, Pune. She has also been involved in training of students in Clinical Research.

Dr. Arun D. Bhatt
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Dr. Arun Bhatt is an MD in Medicine from Mumbai, and has vast experience in the Pharmaceutical industry. He has worked for Ciba Geigy, and Novartis as the Medical Director. Dr. Bhatt is member of numerous professional bodies and is the Joint Editor-in-Chief of the only Indian Journal in the field of Clinical Research (Perspectives in Clinical Research). He is a scientist par excellence and has over 100 publications in Indian and international journals.

Ms. Ekta Kalra
M.Sc.

A microbiologist with diploma in Biotechnology, Clinical Research, Patents and Regulatory Affairs, Ekta has been a Clinical Data Manager at Tata Consultancy Services. She was also a lecturer and research guide for Graduate and Post graduate students at KC College, Mumbai and visiting faculty at Fergusson College and Modern College, Pune. She has worked as faculty for Clinical Research at Bilcare Research Academy, Pune. She was also involved in corporate training. She has research articles published in international journals, textbooks and magazines.

Dr. Deepa Subramanian
MBBS, MSc, PGDPM

Dr. Deepa Subramanian is a medical graduate from JJM Medical College Davengere. She has done her M.Sc. in Clinical Research from Cranfield University, UK and Post Graduate Diploma in Pharmaceutical Management from Institute of Clinical Research India.

She has more than three years of experience in clinical practice working in hospitals in Kerala, Pune and Bangalore. She has vast experience in clinical research industry with specific expertise in managing phase1 to phase 3 trials. She has managed Observational and Interventional studies in various domains such as Ophthalmology, Gastroenterology, Rheumatology, Diabetes Mellitus, Respiratory disease and Oncology. She has experience in handling global trials and multi-centric trials. She has been instrumental in setting up a CR company “Syncretic Clinical Research Services” in Bangalore, Karnataka - India.

Contributors' Profile...

Suresh Kumar Karri
M. Pharm, MBA

Suresh Kumar Karri is a Post graduate in Pharmaceutical Sciences with Pharmacology as a specialization; he has also done his MBA in International Business and is a certified professional in Intellectual Property Rights from WIPO, Geneva. He is a member of various Pharmaceutical Associations; both at National and International levels, like IPA, FIP and IPS to name a few; he has two International journal publications to his credit. He has vast experience in clinical research, and is one of the few professionals in India who has hands on experience in bioequivalence and phase trials as well. He has served as visiting faculty in a few Clinical Research Institutes based in Bangalore and still provides his services as a visiting faculty in one of the CR institutes Bangalore.

Dr. Hemali Premji

Dr. Hemali Premji is currently heading Quality and Compliance at Boehringer-Ingelheim India Pvt. Ltd. Prior to this, she was Head, Clinical Research Management at Sanofi-Synthelabo India Pvt. Ltd. She has worked in the field of clinical research in India and US for several years covering a wide spectrum of roles from hands-on operations to management at Investigator sites, CROs, SMOs and Pharmaceuticals.

Ms. Manjiri Joshi
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Ms. Manjiri Joshi is a pharmacist with management qualifications. She has wide experience in sales, marketing and management having worked in the Pharmaceutical, clinical research industries and in academics. She presently heads the operations at Jehangir Center for Learning where she is the Director.

Dr. R. B. Ghooi
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Dr. Ghooi is a pharmacologist who has worked both in preclinical and clinical phases of drug development. He has been teaching Clinical Research first at ICRI and then at Bilcare Research Academy. Presently he is the professor of Drug Discovery and Clinical Research at Symbiosis International University in Pune. Dr. Ghooi has wide experience in the pharmaceutical and CRO industry, he is also the author of a book “Essentials of Clinical Research” published in 2010, and has over 40 research papers to his credit.

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Dr. Ritushree Kukreti
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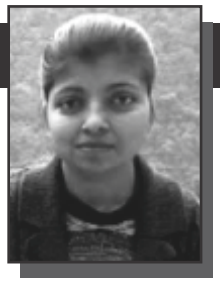
Dr. Ritushree Kukreti is Ph.D. from Department of Biosciences and Biotechnology, Roorkee University (the present IIT Roorkee). Later she joined University of Paris, France for her postdoctoral work and in 1998 joined the Functional Genomics Unit at CSIR-Institute of Genomics and Integrative Biology, Delhi, India. Subsequently, in Oct. 2002 she joined Nicolas Piramal India Ltd. as a Senior Scientist. Currently, she is a scientist at CSIR-IGIB working towards understanding the genetic and molecular basis of disease severity, variable drug response for complex diseases and related studies to create a powerful platform for pharmacogenomics driven drug discovery clinical medicine. She is working in the area of pharmacogenomics and has achieved success in establishing this research area in the institute generating high impact knowledge. Her aim is to identify genes and interacting genetic factors that contribute to disease and drug responses. This involves study of metabolic pathways and gene-gene interactions by using multiple linear regression analyses for the establishment of significant associations between genetic variants and phenotypes of biomedical importance.



Meenal Gupta
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Meenal Gupta is currently working under the guidance of Dr. Ritushree Kukreti at Institute of Genomics and Integrative Biology (IGIB), Delhi, India. She has completed her graduation in Microbiology from Delhi University and postgraduation in biotechnology from H.N.B Garhwal University. Her research interests include the elucidation of pharmacogenomic signatures to develop predictive model for drug response outcomes. Her work has led to publication of 4 research articles in international journals.

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Dr. Jadhav
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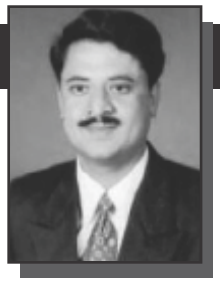
Dr. Jadhav has completed her Doctorate in Pharmacy from K. M. Kundnani College of Pharmacy, Mumbai; and holds a Diploma in Clinical Research and also Quality Management. She has a collective and extensive experience of over 20 years spread over academics and clinical research. Her clinical research experience includes successful management of various roles and responsibilities in different capabilities while executing phase I-IV studies, viz. Project Management, Pharmacovigilance, Clinical Trial Supplies Management, Training and Development, Line Management, establishing/operationalizing Quality Management Systems and Quality Assurance.

She has been associated with leading Pharma Companies like Sanofi-Aventis and Vanthys Pharmaceutical Development (a JV of Eli Lilly, USA & Jubilant Life Sciences) where she held senior positions and managed large teams. She currently serves Karmic Lifesciences as the Senior Associate Director, Clinical Operations.



Dr. S. R. Pattan
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Dr. S. R. Pattan did his B. Pharm/M. Pharm/Ph.D from KLE's College of Pharmacy, Belgaum. He has published more than 200 research/review articles in reputed national/international journals. He has received best reviews award for the title 'The recent developments on COX-2 inhibitors.' Published in Indian drugs, December 2008 by IDMA. He is been recognized by Marquies WHO's WHO of biographical society of UK for outstanding contribution in the field of pharmaceutical science/technology. He has 2 patents to his credit and has conducted many seminars. Presently working as Principal of Pravara Rural College of Pharmacy, Loni and Additional Secretary of Pravara Rural Education Society, Loni, he is an excellent researcher in the field of Medicinal Chemistry.

Soumi Duttagupta
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Soumi Duttagupta has 10 years of experience in the clinical research industry. She has worked as a medical writer in internationally reputed companies like Glaxo Smith Kline Beecham, Clin Tec International and Lotus Labs, and is currently working as a freelance medical writer. She has expertise in preparing a wide range of regulatory and medico marketing documents in various therapeutic fields like Immunology/Vaccines, Infectious Disease, Oncology, Dermatology and Endocrinology. An ACRP (Association of Clinical Research Professional) certified trainer, she has 5 years of experience in training aspiring students on various aspects of clinical research and conducting corporate trainings for Clinical Research Associates and Project Managers.

CONTENTS

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Chapter … 1

ORIENTATION TO DRUG RESEARCH

"Advances in medicine and agriculture have saved vastly more lives than have been lost in all the wars in history." **Carl Sagan**

NOMENCLATURE AND STANDARDS FOR DRUGS

Introduction

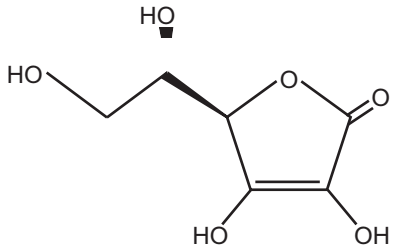
In order to meet the multiple objectives of conformity, standardization, esoteric values of manufactures, research and replication and quality assurance, drugs are classified into various groups.

Objectives

1. To discuss the accepted approach to drug classification.
2. To distinguish between the various drug names; chemical, generic and trade.
3. To identify the reason for the preference of generic names of drugs over their chemical and trade names.

Drug Nomenclature/Naming of Drugs

This is a system of classification of drugs. The three name classifications of drugs are: the Chemical/Molecular/Scientific name, the Generic or Non-Proprietary name, and the Brand or Trade or Proprietary name.



Chemical names; convenient components for laboratory inventions and replication; assures quality, Image provided by courtesy of commons-commons.wikimedia.org

- **Chemical Name:** It depicts the chemical/molecular structure of the drug in terms of atoms and molecules accompanied by a diagram of the chemical structure. They are long and can be clumsy and are useful to only a select few, technically-qualified personnel. For

example, acetyl-p-amino-phenol is the chemical name for Paracetamol and the image above gives the structure of Vitamin C.

- **Non-Proprietary/Generic/Approved Name:** This is the abbreviated and approved name of the drug. It is the official medical name assigned by the producer in collaboration with the Food and Drugs Board and the Nomenclature Committee. Since they have the same chemical structure, generic names may be used by any interested organisation irrespective of the manufacturer and also helps to avoid the dilemma of naming the drug. A generic drug name is not capitalized; for example, aluminum hydroxide.
- **Proprietary/Trade/Brand Name:** These are names given to the drug by the manufacturing and marketing company. They are copyrighted terms selected by a manufacturer to designate a particular product. Copyright laws prevent any other person or entity from using the name, and other laws prevent pharmacists from substituting chemically-identical products for the trade name article. In most cases, one drug could have many trade/brand names e.g. Acetaminophen has about 30 trade names. Some of them are Tylenol, Paramol, Panadol, Calpol etc.

DEFINITIONS IN PHARMACOLOGY

1. **Absorption:** The movement of drug particles from the GI tract to body fluids.
2. **Active absorption:** Requires a carrier, an enzyme or a protein to move the drug against a concentration gradient.
3. **Adverse reactions:** More severe than side effects, always undesirable.
4. **Agonists:** Drugs that produce a response.
5. **Antagonists:** Drugs that block a response.
6. **Bioavailability:** (Subcategory of absorption) the percentage of a drug that reaches systemic circulation.
7. **Disintegration:** The breakdown of a tablet into smaller particles.
8. **Dissolution:** The dissolving of smaller particles in the GI fluid prior to absorption.
9. **Distribution:** The process by which a drug becomes available to body fluids and body tissue.
10. **Duration of action:** The length of time the drug has a pharmacologic effect.
11. **First-pass effect:** The process in which a drug passes to the liver first.
12. **Half-life:** The time it takes for one-half of the drug concentration to be eliminated; a drug goes through several half-lives before 90% of the drug is eliminated.
13. **Loading dose:** Large initial dose given to achieve a rapid minimum effective concentration in the plasma.
14. **Onset:** The time it takes to reach the minimum effective concentration (MEC) after a drug is administered.
15. **Passive absorption:** Occurs mostly by diffusion.

16. **Peak action:** The point at which a drug reaches it's highest blood or plasma concentration.
17. **Peak drug level:** The highest plasma concentration of a drug at a specific time.
18. **Pharmaceutics:** The first phase of drug action.
19. **Pharmacodynamic phase:** The study of drug concentration and it's effects on the body.
20. **Pharmacogenetics:** The effect of a drug action that varies from a predicted drug response because of genetic factors or hereditary influence.
21. **Pharmacokinetic:** The process of drug movement to achieve drug action.
22. **Pinocytosis:** The process by which cells carry a drug across the cell membrane by engulfing the particles.
23. **Protein-binding effect:** The portion of a drug that is bound is inactive because it is not available to the receptors.
24. **Side-effects:** Physiological effects unrelated to desired drug effects.
25. **Therapeutic range:** Drug concentration in plasma should be between the minimum effective concentration in the plasma and the minimum toxic concentration.
26. **Trough level:** The lowest plasma concentration of a drug. The trough level measures the rate at which a drug is eliminated; levels are drawn immediately before the next dose of a drug is given.

ABSORPTION, DISTRIBUTION, METABOLISM AND EXCRETION OF DRUGS

The four processes involved when a drug is taken are absorption, distribution, metabolism and elimination or excretion (ADME).

Pharmacokinetics is the way the body reacts to the drug once it is administered. It is the measure of the rate (kinetics) of absorption, distribution, metabolism and excretion (ADME). All the four processes involve drug movement across membranes. To be able to cross the membranes, it is necessary that the drugs should be able to dissolve directly into the lipid bi-layer of the membrane; hence lipid-soluble drugs cross directly whereas drugs that are polar do not.

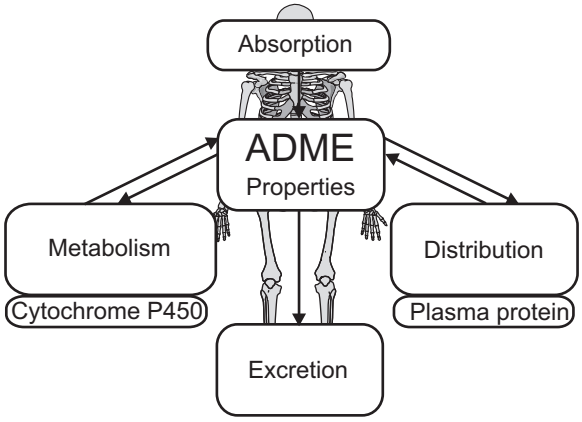


Fig. 1.1: The Interplay between Absorption, Distribution, Metabolism and Excretion (ADME)

(a) Absorption

Absorption is the movement of a drug from it's site of administration into the blood. Most drugs are absorbed by passive absorption but some drugs need carrier-mediated transport. Small molecules diffuse more rapidly than larger molecules. Lipid-soluble non-ionized drugs are absorbed faster. Absorption is affected by blood flow, pain, stress etc.

Acidic drugs such as aspirin will be better absorbed in the stomach whereas a basic drug like morphine will be absorbed better in the intestine. Most of the absorption of the drug takes place in the small intestine since the surface area of the stomach is much smaller than that of the intestine. Most of the drugs are absorbed in the small intestine as the amount of time the drugs spend in the stomach is less and also the surface area of the stomach is small. If a basic drug is taken after a meal, the activity of the drug can be reduced whereas if an acidic drug is taken after a meal the action of the drug can be noticed much more quickly, owing to the gastric absorption.

Even a drug like lipophilic to be absorbed in the intestine, some portion of it needs to be dissolved in the intestinal juices which are aqueous. There are some substances that are partly soluble in water and it is these that will be absorbed followed by an equivalent amount from the undissolved portion. Thus complete absorption takes place in this manner. There are bile salts present in the intestine which aid in salvation of the drug and their resultant absorption. Drugs that are amphipathic have no problem in getting absorbed. There are some drugs that are completely insoluble in water. Such drugs float as globules in the intestine but the bile salts emulsify these into small enough particles such that absorption can take place. e.g. vitamins. Some of the drugs are similar to compounds found in the body e.g. thyroxine and such drugs can be absorbed into the system by active transport.

When drugs are injected into the muscle, subcutaneous layer absorption still has to take place but it is less dependent on the chemical nature of the drugs since the drugs are absorbed into the circulatory system through the small pores in the capillary walls.

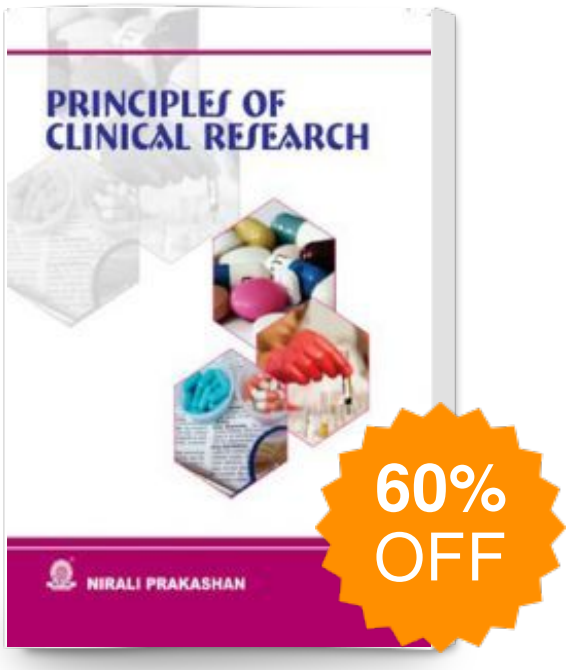
(b) Distribution

Distribution is the movement of drugs throughout the body. Determined by the blood flow to the tissues, it is ability of the drug to enter the vasculature system and the ability of the drug to enter the cell if required.

Plasma Protein Binding

The blood stream has the ability to transport relatively insoluble substances. These substances are transferred by binding to the proteins which have a very amphipathic structure. The hydrophilic group renders the protein soluble in water and the lipophilic compounds are attracted to the lipophilic group and are loosely bound to the protein molecule hence protein-bound. Most of the drugs which travel in the plasma are partly in solution and partly bound to the plasma protein. The bound drug is inactive whereas the unbound drug is active. The ratio of bound to the unbound drug varies. Binding is reversible. Generally, acidic drugs bind to albumin and basic drugs to α_1-acid glycoprotein. Diseased state can adversely impact the effectiveness of the drug. Globin levels in the body increase with age; a factor that should be taken into account when treating an elderly person with a basic drug.

Principles Of Clinical Research



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