

M . P H A R M

PHARMACOLOGY

GOAL: To produce competent Pharmacologists.

OBJECTIVES: Upon completion of the course, the candidate shall have knowledge of understanding the concepts of drug action and its mechanisms involved

Skill: the ability to screen new molecules for their potential pharmacological effects and toxicity

Attitude: the ability to

1. Work independently and as a member of a team
2. Plan his / her work for efficient use of time and resources
3. Identify the cause and to solve the problem
4. Think and evaluate scientifically, ethically and critically

TITLE OF PAPERS

PAPER I	Modern Pharmaceutical Analysis	(T:3Hrs/wk,P:6Hrs/wk)
PAPER II	Advanced Pharmacology and Toxicology	(T:2Hrs/wk, P:6Hrs/wk)
PAPER III	Pharmacological Screening Methods and Clinical Evaluation	(T:2Hrs/wk, P:6Hrs/wk)
PAPER IV	Molecular Biology	(T:2Hrs/wk, P:6Hrs/wk)

List of special equipment

- | | |
|---|-------|
| 1. Student's Physiograph | 3 nos |
| 2. Semi auto Analyzer | 1 no |
| 3. Langendorf's Heart Perfusion Apparatus | 2 nos |
| 4. Students Organ Bath (Temperature Controlled) | 6 nos |
| 5. Elevated Plus Maze | 1 no |
| 6. ECG Equipment for Rats | 1 no |
| 7. Condon's Manometer (for rat BP) | 3 nos |

PAPER II. ADVANCED PHARMACOLOGY AND TOXICOLOGY

Revised Syllabus		Hours
<p>GOAL: To understand the mechanism of drug action in detail and toxicity of drugs.</p> <p>OBJECTIVES: Upon completion of the course, the candidate shall be able to</p> <ul style="list-style-type: none"> - know the chemical mediators and mechanisms by which the drugs act - know the drug therapy of certain disorders - understand gene therapy - understand different types of toxicities 		
COURSE DESCRIPTION		
THEORY	50 Hours (2Hrs/wk)	
<p>a. Molecular Mechanisms in Cell regulation</p> <p>b. Signaling molecules and their receptors:</p> <p>i. Molecules: Nitric oxide, carbon monoxide, neurotransmitters, cytokines, peptide hormones, growth factors and eicosanoids.</p> <p>ii. Receptors:</p> <ol style="list-style-type: none"> 1. Cell surface Receptors: Ion channels, G-protein coupled receptors, tyrosine kinase receptors, cytokine receptors, non-receptor protein tyrosine kinases 2. Nuclear receptors: Steroid hormone receptors, thyroxine receptors, other nuclear receptor families <p>c. Signal transduction:</p> <p>d. Intracellular signal transduction: cAMP, cGMP, IP3-DAG, calcium pathway, PI3K/Akt, m-TOR, MAPK, JAK/STAT, TGFβ/Smad, NFB signaling, Hedgehog-Wnt, Notch pathways including Adrenergic and cholinergic transmissions. Other peripheral mediators: 5-HT and Purines, Cannabinoids, Peptides and proteins</p> <p>i. Cytoskeleton signal transduction: Integrins and signal transduction, regulation of actin cytoskeleton</p>		12
<p>2. Chemical Mediators</p> <p>Biosynthesis, pathophysiological roles, receptors and drugs affecting the receptors for following</p> <p>a. Mediators of inflammation and allergy: Histamine, Bradykinin, PAF, Eicosanoids: prostaglandins, thromboxanes, leukotrienes and related compounds, EDRF and vascular substances, oxygen free radicals, Cytokines, Cox- 1 and Cox-2.</p>		4
<p>3. Pharmacotherapy [28 hrs]</p> <p>The student is expected to understand Pathophysiology, Pharmacotherapy and critical analysis of rational use of drugs in the following disorders.</p> <p>a. Introduction to Pharmacotherapeutics</p> <p>b. CVS: Hypertension, Ischaemic heart disease, CCF, Cardiac arrhythmias and dyslipidaemia. 4 hr</p> <p>c. Respiratory: Asthma and COPD 1 hr</p> <p>d. CNS: Parkinson's disease, Alzheimer's disease, Schizophrenia, Affective disorders, Epilepsy, insomnia, anxiety and pain management 6 hr</p> <p>e. Musculoskeletal: Rheumatoid & Osteoarthritis, hyperuricaemia, Myasthenia gravis. 2 hr</p> <p>f. GIT: Peptic ulcer, GERD, Inflammatory bowel diseases, constipation, diarrhoea. 3 hr</p> <p>g. Endocrine: Obesity, Diabetes mellitus, Osteoporosis, Thyroid and parathyroid disorders, 4 hr</p> <p>h. Infectious: UT infections, RT infections, GI infections (Bacterial and protozoal), Malaria, Tuberculosis, AIDS, Malignant: Leukaemia, Lymphomas and solid tumours.</p>		28
		6

8 hr

4. Toxicity studies: [6 Hours]

- a. Acute, sub-acute and chronic studies: Protocols, objectives, methods of execution and regulatory requirements.
- b. Reproductive toxicology assessment: Male reproductive toxicity, spermatogenesis, risk assessment in male reproductive toxicity, female reproductive toxicology, oocyte toxicity, alterations in reproductive endocrinology, relationship between maternal and developmental toxicity
- c. Mutagenicity: In vitro tests for gene mutations in bacteria, chromosome damage, gene mutations in vivo (micronucleus tests and metaphase analysis) in rodents.
- d. Carcinogenicity studies: In vivo and In vitro studies
- e. Toxicological requirements for biological and bio-tech products: Safety analysis, concept of safety Pharmacology, antibodies, transmission of viral infections, residual DNA

Text Books:

1. Goodman and Gilman's The Pharmacological Basis of Therapeutics. (International Edition) McGraw Hill, New York (2001), 10th Edition.
2. Pharmacology by Rang HP, Dale MM and Ritter JM. Churchill Livingstone, London, 6th Edition, 1999.
3. Basic and Clinical Pharmacology by Bertram G Katzung (International Edition) Lange Medical Book/McGraw-Hill, U.S.A. (2001) 8th Edition.
4. Clinical Pharmacy by D.R. Laurence, P.N. Bennett & Mi. Brown, 8th Edition Churchill Livingstone 1997.
5. Clinical pharmacy and therapeutics –Eric T, Herfindal, Williams and Wilkins Publications
6. Clinical pharmacy and therapeutics –Roger and Walker, Churchill Livingstone Publication
7. Experimental and surgical techniques in the rat, 2nd edition H.B. Waynforth and P.A Flecknell.

Reference Books:

8. Harrison's Principles of Internal Medicine. (2 Volumes 2001) by Braunwald, Fauci, Kasper, Hauser, Longo Jameson, McGraw Hill, New York, 15th Edition.
9. Pharmacotherapy; A pathophysiologic approach-Joseph T. Dipiro et.al Appleton and Lange
10. General and applied toxicology by B. Ballantyne, T. Marrs, P. Turner (Eds) The Macmillan Press Ltd, London.
11. Harrison's Principles of Internal Medicine. (2 Volumes 2001) by Braunwald, Fauci, Kasper, Hauser, Longo Jameson, McGraw Hill, New York, 15th Edition.

Journals:

1. Trends in Pharmacological Sciences. [Essential]
2. Indian Journal of Pharmacology [Essential]
3. Journal of Pharmacology and Experimental Therapeutics [Essential]
4. Indian Journal of Physiology and Pharmacology. (Desirable)
5. Annual Reviews of Pharmacology and Toxicology. [Desirable]
6. Pharmacological Reviews. [Desirable]
7. J-PET Journal of Pharmacology and experimental Therapeutics.

PRACTICALS

1. Animal house: Design and facilities to maintain the animals
2. Routes of administration of drugs like oral, intravenous, intraperitoneal, intramuscular, subcutaneous including conversion of human dose to animal

3. Anaesthetics for animals (isoflurane by inhalation, ketamine+xylazine by intraperitoneal)
4. Blood sampling methods in experimental animals (cardiac puncture, retroorbital, tail vein, cephanous, marginal ear vein)
5. To identify the cholinergic, adrenergic, serotonergic, vasodilator and cardiotoxic drug /blockers using isolated mammalian heart preparation in Langendorff's setup.
6. To assess the effect of drugs on angiogenesis using chorio- allantoic membrane (CAM) assay
7. To identify the Anti-dysrhythmic activity in rats using ECG
8. To identify the effect of various autonomic drugs on rat blood pressure (carotid and jugular cannulation).
9. To identify the effect of various drugs on rabbit/rat/chick jejunum preparation.
10. To identify the Acetylcholine, noradrenaline, adenosine and serotonin like drug /blockers using rat anococcygeus muscle preparation.
11. To identify the following receptors by using suitable tissue preparations:
 - i. the alpha action of a drug
 - ii. the beta action of a drug
 - iii. the muscarinic action of a drug
 - iv. the nicotinic action of drug
 - v. the 5 HT action of a drug

Books for Practicals

1. Fundamentals of experimental pharmacology by M.N Ghosh, scientific book agency, Calcutta.
2. Hand book of experimental pharmacology by SK Kulkarnan, Delhi, Vallabh Prakash
3. Short Protocols in Pharmacology and Drug Discovery edited by Enna SJ, et al., John Wiley & Sons Inc.
4. General and applied toxicology by B. Ballantyne, T. Marrs, P. Turner (Eds) The Macmillan Press Ltd, London.

**PAPER III PHARMACOLOGICAL SCREENING METHODS &
CLINICAL EVALUATION**

Proposed	Hours
<p>GOALS:</p>	
<p>To understand the process of drug development and estimation of drugs using bioassays. To understand and apply pharmacokinetics to rational drug therapy.</p>	
<p>OBJECTIVES: Upon completion of the course, the candidate is expected to know</p>	
<ol style="list-style-type: none"> 1. The regulations and ethics concerning animal studies and experiments on human beings. 2. Carry out screening of new drugs. 3. Participate in drug development process. 4. Know alternatives to animal screening procedures / techniques 5. To perform Bioassays official in IP/BP/USP. 6. Concepts of kinetics and various pharmacokinetic models 	
<p>COURSE DESCRIPTION</p>	
<p>THEORY 50 Hours (2 Hrs/wk)</p>	
<p>1. Drug Design: [6 Hours]</p>	6
<ol style="list-style-type: none"> a. Drug discovery and development – introduction b. Modern methods of drug discovery (Introduction, Target identification, Target validation, Lead compound identification and Optimization). c. Study of laboratory animals including physiological parameters Regulations and ethics requirements. Transgenic animals and other genetically prone animal models (Viz Nude Mice, SH rats and humanized mice). 	20
<p>2. Preclinical models employed in the screening of new drugs belonging to following categories: [20 Hours]</p>	
<p>Antipsychotic agent; Antianxiety agents; Nootropic drugs; Antidepressant drugs; Antiparkinsonian agents; Analgesics; Antiepileptics; Antiinflammatory agents; Antiulcer agents; Antianginals and myocardial infarction; Antiarrhythmics; Antiatherosclerotic drugs; Antimalarials; Antidiabetics; Antihypertensives; Anticancer.</p>	6
<p>3. Modern techniques to elucidate the mechanisms of drug actions: [6 Hours]</p>	
<ol style="list-style-type: none"> a. Cell culture and maintenance: Concepts of in-vitro screening, Different cell lines (animal & human) used in screening techniques. Primary and secondary cultures, Principles of techniques involved in cell culture and its maintenance. b. Introduction and applications of Biomarker analysis c. Introduction to Translational pharmacology d. Alternatives to animal screening procedures, cell-line, patch-clamp technique, in-vitro models. e. High throughput screening (HTS): Introduction, Basic principles involved in cell based assays, receptor binding assays and ultra high through put screening. 	7
<p>1. Definition and</p>	
<p>Scope of Pharmacokinetics. 1 hour</p>	
<p>Absorption, Distribution, Metabolism, Elimination and transporters</p>	
<p>Individualization: variability, genetics, age and weight, disease, interacting drugs, and monitoring of the same. 1 hour</p>	
<p>Pharmacokinetic models: compartmental models, noncompartmental models and physiologic model. Nonlinear pharmacokinetics, multiple dosing and dosage regimen.</p>	3

Clinical Research: Introduction and Ethics [3 Hours]

- a. Definition and scope of clinical research. Role of sponsor, study director or principal investigator; Clinical Research Associate in conduct of Clinical Research
- b. Study design, ethics in patient selection and preserving their rights. Institutional Ethics Review committee its constituent members and its role in clinical research. Introduction to informed consent and its importance.

3

4. Phases of Clinical Trial and Clinical Trial Design [3 Hours]

- a. Calculation of Human Equivalent Dose; Phase 0, Phase I, Phase II, Phase III, Phase IV and Phase V Clinical trial.
- b. Randomized Clinical Trial, Uncontrolled Trials, Protocol Development, End points, Patient Selection and blinding, special designs like cross over design, factorial design, Equivalence design, confounding in clinical trials and ways to minimize it, Missing data and its management, occurrence of ADRs, interim monitoring and stopping of trials,

5

5. Regulatory Affairs in Clinical Research [5 Hours]

- a. Pharmacovigilance
- b. Laws governing Clinical Research: preparation of Drug master files (IND, NDA and ANDA) Schedule Y, Code of Federal Regulations (CFR-USFDA) CDSCO (ICMR), EMEA
- c. International Guidelines to meet the standards in Clinical Research: ICH guidelines for efficacy testing of drugs: clinical aspects and data management strategies (E1 – E14]

BOOKS:

1. Drug Discovery and Evaluation Pharmacological Assay by Vogel H G and Vogel W H (Springer publication)
2. Evaluation of drug activities Pharmacometrics by D R Laurence and A L Bacharach Vol. 1 and 2.
3. Drug Screening Methods by SK Gupta, Jaypee Brothers, New Delhi.
4. Alternatives to animals in toxicity testing. Scientific American 26:(1989), 16-22.
5. Remington's Pharmaceutical Sciences 24th edn.
6. Methods of clinical trials by Alan Spreit and Simon.
7. Clinical Pharmacology by P N Bennett and Brown
8. The Oxford textbook of Clinical Pharmacology and drug therapy by D.G. Graham-Smith and J.K.Aronson.
9. Modern Methods of Drug Discovery by Hillisch, A and Hilgenfeld, R

Reference Books:

1. Short Protocols in Pharmacology and Drug Discovery edited by Enna SJ, et al., John Wiley & Sons Inc.
2. Modern drug research- Paths to better and safe drugs (Medicinal Chemistry vol. 9) by Y C Martin, E. Kutter and V. Austel
3. Practical approaches in toxicity studies by Poole and Leslie
4. Pharmacological Experiments in Intact preparations, Edinburgh University Pharmacology staff, Livingstone, (1968)
5. Pharmacological Experiments on Isolated preparations, Edinburgh University Pharmacology staff, Livingstone, E & S Livingstone Edinburgh & London (1970).
6. Screening Methods in Pharmacology, Academic Press, New York and London (1965).
7. Biopharmaceutics and Clinical Pharmacokinetics by Milo Gibaldi, Lea and Febiger Book. 3rd Edition (1984).

Journals:

1. Indian Journal of Pharmacology [Essential]
2. British Journal of Pharmacology.

3. Drug Metabolism and Pharmacokinetics.

Practicals : [6 hours/week]

1. Bioassay of acetylcholine/histamine using guinea pig/rat ileum preparation.
2. Bioassay of oxytocin using rat uterine preparation.
3. PA_2 values of various antagonists using suitable isolated tissue preparations.
4. *In-vitro* Absorption study using Inverted rat intestine
5. Exercise on determination of pharmacokinetic parameters using UV/visible spectrophotometer/HPLC
6. Screening of anxiolytic drugs
7. Screening of antidepressant drugs
8. Antipyretic activity by yeast induced pyrexia in rats.
9. Anti-inflammatory activity by rat paw oedema method.
10. Analgesic by hot plate, tail flick, tail dip, paw pressure test, plantar test and/or writhing methods.
11. Skeletal muscle relaxant activity by rotarod method.
12. Anticonvulsant
13. Pole climbing
14. Actophotometer
15. Exercise on Biostatistics using software
16. Enzyme based *in vitro* bioassays (5-LO, COX, DPPH, AchE, hyaluronidase inhibition assays)
17. Antioxidant activity of Super oxide dismutase (SOD), Catalase, lipid peroxidation and Reduced glutathione in tissue homogenate

PAPER-IV. MOLECULAR BIOLOGY

Proposed	Hours
<p>GOALS: To understand the cell biology & genetics that forms the basis for new drug discovery.</p> <p>OBJECTIVES: Upon completion of the course, the candidate is expected to know basic cell biology. Recombinant DNA technology, transfer of genes to mammalian cells.</p> <p style="text-align: center;">COURSE DESCRIPTION</p> <p>THEORY</p> <p>1. Cellular structure and functions: (8 hours)</p> <p>a. Cell structure: cell wall, cytoplasm and its components, nucleus and its components</p> <p>b. Plasma membrane: Structure, transport of small molecules and drugs across it, endocytosis, transport proteins and their inhibitors</p> <p>c. Extra cellular matrix, cell signaling and communication between cells and their environment, ion-channels, Organization of signal transduction pathways, third messengers,</p> <p>d. Biosensors-introduction and applications.</p> <p>2. Mechanisms of Cellular Regulation: (10 hours)</p> <p>a. Excitation, contraction and secretion</p> <p>b. Cell proliferation: Phases and checkpoints of Cell cycle, Positive and negative regulators of cell cycle</p> <p>c. Cell renewal: Stem cells and maintenance of adult tissues, proliferation of different stem cells, medical application of adult stem cells, embryonic stem cells, somatic cell nuclear transfer, induced pluripotent stem cells and their therapeutic applications in medicine.</p> <p>d. Cell death (Apoptosis): Events of apoptosis, regulators of apoptosis, intrinsic and death pathways of apoptosis.</p> <p>e. Animal cell culture</p> <p>3. Gene manipulation and its applications (32 hours)</p> <p>a. Role of genes within cells, DNA- the primary genetic material, Elucidation of genetic code, Gene expression, Genetic elements that control gene expression, microarray. (5 hrs)</p> <p>b. Recombinant DNA Technology: Principles, process and applications. Gene cloning: Isolation, cloning vectors, enzymes used in molecular cloning, PCR (Polymerase chain reaction), LCR (Ligation chain reaction) and their applications. The formation and uses of RFLP's (Restriction Fragment Length Polymorphism). (8 hrs)</p> <p>c. Recombinant DNA / Human Genetics: DNA sequencing, Mapping and cloning of Human disease genes, DNA-Based diagnosis of genetic diseases. (4 hrs)</p> <p>d. Human genome project. (1 hrs)</p> <p>e. Gene therapy and Antisense technology (2 hrs).</p> <p>f. Biotechnology related techniques: Protein engineering, Peptide chemistry and peptidomimetics, Nucleic acid technologies, catalytic antibodies, glycobiology. (6 hrs)</p> <p>g. Principles of cell based assays and their application: MTT assay, COMET assay, DNA ladder, Radio-ligand binding assay, RT-PCR, Western blotting, Immunoblotting, Immunofluorescence, Flow cytometry. (6 hrs)</p> <p>BOOKS:</p> <p>1. Molecular biology of the CELL. Alberts B. et.al (Eds). Garland Publishing Inc.</p>	<p>8</p> <p>10</p> <p>32</p>

New York and London.

2. Pharmaceutical Biotechnology. Crommelin DJA and Sindelar RD. (Eds). Harward Academic Publishers, Australia, UK.
3. Biopharmaceuticals: Biochemistry & Biotechnology. Gary Walsh. (Eds). John Wiley and Sons.
4. Recombinant DNA. James D. Watson, Michael Gilman, Jan Witowski, Mark Zollet (Eds). Scientific American Books, New York
5. The Cell: A Molecular Approach. Geoffrey M Cooper and Robert E Hausman (Eds). 5th ed
6. S P Vyas and D V Kohli, Pharmaceutical Biotechnology
7. Kumarsan
8. Satynarayan

PRACTICALS

(6 Hrs/wk)

1. Drug mutagenicity study using mice bone-marrow chromosomal aberration test.
2. Drug mutagenicity study using mice bone-marrow micronucleus test.
3. Ame's test (Salmonella typhimurium)
4. Drug cytotoxicity using a cell line (MTT or any other assay)
5. Polyacrylamide Gel Electrophoresis
6. Western Blotting.
7. Isolation and estimation of DNA and RNA.
8. Restriction digestion of DNA.
9. Ligation of DNA.
10. Isolation of plasmids.
11. Estimation of proteins by Bradford /or Lowrays

Scheme or examination:

Synopsis	20 marks
Major experiment	35 marks
Minor experiment	25 marks
Viva-voce	20 marks
Total	100 marks