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Review Article

A review on experimental pharmacology

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ABSTRACT

In this era where the pharmaceutical companies and products are hiking in its need and production it is inevitable to document the safety and toxicity along with the indications of the same. This is where the experimental study has a vital role to play. Experimental pharmacology is the science where the drug interaction with different receptors and target sites in living organism are explained. This article reviews about the different aspects of experimental pharmacology and its uses.

Keywords: Experimental pharmacology, products, dosage

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INTRODUCTION

Pharmacology a unique branch of biology, deals with the study of drugs, where a drug can be defined as a man-made natural or endogenous molecule which exerts a biochemical or physiological effect on cells, tissues or organs. To be more specific it is the study of interactions that occurs between a living organism and chemicals that affect normal or abnormal biochemical functions. It is also expounded as the discovery of new drug or to study the action of an existing one.

Experimental pharmacology implicates the study of pharmacology through bioassay or to test the effect of various pharmacological agents on different animal species.

History of Pharmacology

2500 years ago during 17th century in Greek experiments were done on Willow leaves. 17th to 18th cent Salicylic acid was tested on willow leaves. 1899 - Bayer marketed Acetyl salicylic acid (Aspirin). 1970- Mechanism of inhibition of

prostaglandin synthesis via Cyclo oxygenase cox enzyme. Rudolf Buchheim is known as the founder of experimental pharmacology. Oswald Schmiedeberg the founder of modern pharmacology¹.

Basics of Experimental Pharmacology

It consists of three elements: subjects, treatment and efficacy. Treatment is again divided as primary, secondary and tertiary.

Three Principles of Study Design

Randomization- to avoid subjective bias in research

Replication- number of times the experiment repeated under same conditions and number of samples used in experiment

Control- self-control design, block control design or case design

Design of Sample Size

Empirical method for determination of sample size:-

Sl. No.	Animals	Quantitative	Qualitative
1.	Mouse, rat, frogs, fish	>/=10	>/=30
2.	Guinea pig, rabbit	>/=6	>/=30
3.	Cat, monkey, sheep, dog	5-10	

Statistical methods: Considering the Confidence level (larger the confidence level larger would be sample size), based on the significance level (usually 5%), variability in the measurements.

Design of Drug dosage: The designing of drug dosage are based on pilot experiment or references, use wide dose interval to determine effective dose range, use regular dose interval when observe dose-effect relationship, use drug equivalent to compare potency of drugs LD50, ED50, EC50, etc. and Dose response curve .

Experiments used for Protocol ²

- Psychopharmacological studies
- Study of analgesics
- Bioassay of various hormones such insulin, oxytocin, vasopressin
- Study of estrus cycle, mating behavior, lactation
- Isolated tissues preparations
- Chronic study
- Gastric acid secretion
- Hepatotoxicity studies
- Study on mast cells

Different Protocols for Experimental Studies

1. Central Nervous System:

Gross behaviour field, Behaviour despair test, Locomotor activity test, Anti- convulsion test electric shock and PTZ model, Reserpine induced catatonic test, D-Amphetamine, induced stereotype test, Oxetremine induced tremors test, Hypotonic potentiating test, Passive avoidance test (Cocks pole climbing test), Skeletal muscles relaxant test, Grip strength test, Anti-anxiety test (zero maze test, plus maze test), Morris water maze test, CALICIT (Carotid artery ligation induced cerebral ischemia test), EEG of rat and mice. Aluminium chloride induced neurodegenerative study

2. Analgesic Study:

Eddy's hot plate test, tail flick test, Formaldehyde induced chronic pain model, Acetic acid induced writhing test

3. Anti-inflammatory Study:

Carrageenan induced acute inflammatory test, Cotton peltate implantation test, Freund's adjuvant induced arthritis test

4. Antipyretic Study:

Yeast induced fever model

5. Gastrointestinal Tract:

Castor oil induced anti diarrhoeal test, Appetite and metabolic test, Vipaka test, Swimming endurance test, Intestinal motility test (charcoal meat test), Anti- ulcer test-pyloric ligation test (stress induced ulcer test), Acetic acid induced ulcerative colitis, Intestinal cytoprotective activity (induced by Methotrexate)

6. CVS and Diuretic Experiments:

ECG of rat and mice, Hyperlipidemic study, Diuretic test, nephroprotective test, Kidney function test, Cardioprotective activity against Isoprenaline induced Myocardial infarction

7. Wound Healing Test:

Burn wound healing test, Dead space, Excision and incision wound healing

8. Toxicity Study:

Acute toxicity study, Subacute toxicity study, Chronic toxicity study

9. Anti- Fertility Test:

Spermatogenesis modulation tests, Oestrous cycle monitoring test

10. Additional Experiments:

Antioxidant test, Isolated tissue experiments, Electrophysiology of isolated tissues, Hormonal assay, Histopathology of organs, Liver function test, Anaemic test (Mercuric chloride & phenylhydrazine induced anaemia), Antivenom test, Antidote poisoning activity, anti-diabetic activity, Galactogenic activity, immunomodulatory activity

Commonly used animals³

Name	Latin Name	Experimental uses	Isolated Tissues/ Organs	Features	Strains used
Rats	Rattus norvegicus	CVS,CNS, reproductive, physiology, GIT, antiulcer activity, anti- inflammatory activity, toxicity study, spermatogenic activity	uterus, stomach, colon, vas deferens brain, rectus abdominalis muscle, rarely brain	Small in size (200g), Drug required in small quantity, Vomiting center absent- drug can be administered orally, Obvious division of stomach into two parts, Gallbladder and tonsils absent (continuous flow of bile into intestine; this facilitate the study of drugs acting on bile, cholesterol reabsorbing etc). Rats being omnivorous resemble man.	Charles foster, Wistar rats, Fischer 344, long evans, Holtzman

Mouse	Mus musculus	Acute toxicity (Zn, Hg, Pb, I, etc.), pesticide aflatoxin toxicity, bioassay of insulin, analgesic test, CNS activity drug, effect of formulations and carcinogenesis, cancer and nutritional research	Ileum and vas deferens	similar to rat, 25-30g in weight, sensitive to almost all test drugs	C57BL/6, BALB/c, A/J, CD1
Guinea pigs	Cavia porcellus	Antihistamine activity, bronchodilator study, hearing activity test, immunological study, allergic study, tests related to amoebiasis and cholera	Ileum, vas deferens, heart, rarely aorta	Docile in nature, more sensitive to histamine, 400-600g weight, tailless	Albino guinea pig, hartley
Monkey	Macaca mulatta	Can be used in almost all protocols (structurally, functionally, phylogenetically closest to humans), virology, parasitology, immunology, nutrition		Subhuman primates, expensive and difficult to breed, not usually used for routine pharmacological testing	Rhesus monkey, bonett, langurs
Rabbits	Oryctolagus cuniculus	Pyrogen testing, skin toxicity and embryological teratogenicity, serological works in contraceptive development, reproductive physiology specially assess ovulation, hyperlipidemia, hypoglycemic activity	Heart, ileum, duodenum	non cyclic ovulators (ovulates only in the presence of male), docile, resistant to atropine (contains Atropine esterase enzyme), coprophagic	Belgian white, New Zealand white
Frogs	Rana tigrina	Learn the muscle nerve preparations and ciliary movements, pregnancy assay, CVS related bioassay	Heart, rectus abdominalis	small in size, easily available, three chambered heart, substance like epibatidine are obtained from frogs, camouflage is a common defensive mechanism, breathe through the highly oxygen permeable skin	Marsh frogs, pool frogs, Rana esculenta (edible frog), Xenopus laevis commonly for pregnancy assay
Cat	Felis catus	Drug effect on blood pressure and respiration on anesthetized animal, physiology of CVS	Nictitating membrane, Kidney and Liver	has well developed nictitating membrane, develops excitement with morphine, develops Methemoglobinemia with intake of acetanilide ⁴	
Dog	Canis familiaris	Similar tests done to cats as these are structurally and functionally similar, assess diuretic activity and hypertension	Chronically prepared fistula and pouches (for gastric secretory study), intestinal tissues	trained easily, used for conditional and reflex experiments	Mongrels, beagles, stray dogs
Hamster	Mesocricetus auratus	virology, cancer research, nutritional research	cheek pouches (graft experiment and anticancer study)	short chunky body, putty tail and shrotles, has large cheek pouch (immunologically inert)	Golden hamster, yellow hamster
Armadillo	Dasypus novemcinctus	Leprosy research, test for cancer causing agents, organ transplant experiments, drug metabolism	skin	Animals produce up to four identical offsprings, nine banded armadillo commonly	Nine banded armadillo ⁵

				used.	
Zebra fish	Danio rerio	Vertebral development study and genetics (mainly in early 1970), embryonic development ⁶	Eggs	freshwater native, lifespan of five years (helps in long term study)	

1. Genetically modified rats – Wistar rats, Sprague Dawley rats, Biobreeding rats, RCS (Royal College of Surgeons) rats, Long evans rats, RCS rats, Shaking rat Kawasaki, Hairless rats

2. Other creatures used for experimental study are Chicken, Pigeon, etc.

Care and Handling of Lab Animals⁷

Animals are to be handled with utmost care and with due regards to their health and wellbeing. Even Euthanasia has to be done in humane method. Indian National Science Academy (INSA) guidelines are to be followed by all research institutions on animal care.

Breeding Types⁸

Inbred Strains: This method helps to reduce heterozygous individuals for any one gene pair and to increase number of homozygous for one or the other member of gene pair. The main drawback of this method is that the animals become unhealthy and more susceptible to diseases. The reproductive capacity also reduces.

Random breeding: Random breeding without regards to their parentage or relationship, with respect to the pedigree.

Selective breeding: Based on the desired character individuals are chosen; for example, if the response towards a drug is to be tested, individuals showing greatest response to it, is chosen.

Breeding Methods⁹

Hand mating: male and female brought together for certain period of time, and separated after mating.

Pair mating: male and female animals are left together even after mating for the rest of their life.

Trio mating: one male is left for mating with two females.

Harem mating: a single male is made to mate with four females. The male is separated as soon as pregnancy detected in female and replaced by another female.

Factors affecting nature and Degree of Pharmacological responses¹⁰

Species: Ex. Guinea pigs and humans are 500 times more sensitive to histamines than rats and mice.

Strains: Ex. presence of hydrolyzing enzymes in the serum and liver of rabbits, make it resistant to Atropine.

Sex: The growth rate is faster in males than in females.

Excessive exposure to chloroform leads to renal lesions in male mice.

Age: LD50 of newborn rats to Phenobarbitone is about 1/3rd that of adults.

DISCUSSION

With the rising demand for medicines, there is a surge in the number of pharmacies and pharmaceuticals which in turn escalates the need for the products to be approved. For clinical trials in humans, the safety and efficacy of the drug should be demonstrated and documented, the effect of different drugs are tested through animal experimental models, experimental pharmacology and preclinical pharmacology. Experimental pharmacology or any animal experiments are to be carried out following the basic guidelines declared by OECD, CDSCO and AYUSH. These guidelines explain about the care and precautions to be taken during an experimental study and the details of how these trials or experiments are to be carried out.

CONCLUSION

Experimental Pharmacology is an important step for drug discovery and before the drug is taken up for clinical research. Various guidelines have been given for the experimental studies to be carried out by OECD, CDSCO, etc. The guidelines ensure the diligent handling of animals, protecting the unethical use and also set plans for the study to be carried out in the specified and standard way. Different study protocols and different species of animals for various study put forth help in carrying out the studies to get the result and evaluate it diligently for further research.

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