Faculty of Pharmaceutical Sciences

Rama University Kanpur (U.P)

BP-404 T PHARMACOLOGY- 1(Theory)
B.PHARM 4th SEM.

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General Pharmacology

Introduction to Pharmacology- Definition, historical landmarks and scope of pharmacology, nature and source of drugs, essential drugs concept and routes of drug administration, Agonists, antagonists(competitive and non competitive), spare receptors, addiction, tolerance, dependence, tachyphylaxis, idiosyncrasy, allergy..

INTRODUCTION TO PHARMACOLOGY-

DEFINITION-

Pharmacology is the science of drugs (Greek: Pharmacon—drug; logos—discourse in). In a broad sense, it deals with interaction of exogenously administered chemical molecules with living systems, or any single chemical substance which can produce a biological response is a 'drug'. It encompasses all aspects of knowledge about drugs, but most importantly those that are relevant to effective and safe use for medicinal purpose.

The two main divisions of pharmacology are pharmacodynamics and pharmacokinetics.

Pharmacodynamics (Greek: dynamis—power) —What the drug does to the body. This includes physiological and biochemical effects of drugs and their mechanism of action at organ system/subcellular/macromolecular levels, e.g.—Adrenaline → interaction with adrenoceptors → G-protein mediated stimulation of cell membrane bound adenylyl cyclase → increased intracellular cyclic 3′,5′AMP → cardiac stimulation, hepatic glycogenolysis and hyperglycaemia, etc.

Pharmacokinetics (Greek: Kinesis—movement)—What the body does to the drug. This refers to movement of the drug in and alteration of the drug by the body; includes absorption, distribution, binding/localization/storage, biotransformation and excretion of the drug, e.g. paracetamol is rapidly and almost completely absorbed orally attaining peak blood levels at30–60 min; 25% bound to plasma proteins, widely and almost uniformly distributed in the body (volume of distribution ~ 1L/kg); extensively metabolized in the liver, primarily by glucuronide and sulfate conjugation into inactive metabolites which are excreted in urine; has a plasma half life (t½) of 2–3 hours and a clearance value of 5 ml/kg/min.

NATURE AND SOURCES OF DRUG-Drug (French: Drogue—a dry herb) It is the single active chemical entity present in a medicine that is used for diagnosis, prevention, treatment/ cure of a disease. This disease oriented definition of drug does not include contraceptives or use of drugs for improvement of health. The WHO (1966) has given a more comprehensive definition—"Drug is any substance or product that is used or is intended to be used to modify or explore physiological systems or pathological states for the benefit of the recipient." The term 'drugs' is being also used to mean addictive/abused/illicit substances. However, this restricted and derogatory sense usage is unfortunate degradation of a time honoured term, and 'drug' should refer to a substance that has some therapeutic/diagnostic application.

SCOPE OF PHARMACOLOGY andHISTORICAL LANDMARK-

A. History –

It is of intellectual interest to the physician to know how drugs are discovered and developed. Often in the past, this was based on folklore or intelligent observation (e.g. digitalis leaf, penicillin). Nowadays, new drugs are mostly developed by the organic chemist working with a pharmacologist, increasingly from basic knowledge about key molecular targets. Usually some sort of biological screen is used to select among organic molecules for optimum pharmacological activity.

1. Francois Magendie (1783-1855), a French physiologist laid down the dictum "Facts and facts alone are the basis of science." Experimental procedures with animals are the testing grounds for determination of drug action.

2. Claude Bernard (1813-1878) worked in Magendie's lab, investigated the plant extract curare and proposed a site of action for this agent.

3. Rudolph Buchheim (1820-1879). In 1847 Buchheim established the first laboratory devoted to experimental pharmacology in the basement of his home in Dorpat which is known as the cradle of experimental pharmacology.

4. Oswald Schmiedeberg (1838-1921). In 1872 Schmiedeberg set up an institute of pharmacology in Strasbourg, France (Germany at that time) which became a mecca for students who were interest in pharmacological problems.

5. J.N. Langley (1852-1925 and Sir Henry Dale (1875-1968) pioneered pharmacology in England, taking a physiological approach.

6. John J. Abel (1857-1938) established the first chair of pharmacology in the U.S.A. (U. Michigan, 1891) after training in Germany. Able went to Johns Hopkins in 1893, and trained many U.S. pharmacologists. He is known as "The Father of American Pharmacology".

7. The second world war was the impetus for accelerated research in pharmacology (the war time antimalarial program) in the U.S., and introduced strong analytical and synthetic chemical approaches.

B. Chemistry –

Chemical structures of drugs can provide information about mechanism of action, pharmacokinetics, stability, and metabolic fate

. 1. Structure-Activity Relationship - A modification of the chemical structure of a drug may accentuate or diminish its pharmacological effects, often providing clues as to the mechanism of action. A picture of the biological reactive site (the receptor) can be developed in such studies. Also, drugs are metabolized by body systems, which may convert the parent drug to a more active or a less active form. The drug structure can be modified to enhance or diminish the rate of metabolic conversion.

2. Sites of Action - The organ or cellular target of drug action.

3. Drug Receptors - Macromolecules in cells or cell membranes with which drugs interact to exert their effects. Usually the interacting forces are reversible ionic and Van der Waals bonds of relatively low energy, but sometimes covalent bonds are formed (e.g. organophosphate insecticides).

C. Pharmacodynamics –

The effect of the drug on the body. Pharmaco-dynamics is the study of the relationship of drug concentration and the biologic effect (physiological or biochemical).

D. Pharmacokinetics –

The effect of the body on the drug. To produce its characteristic effects, a drug must be present in appropriate concentrations at its sites of action. Thus, it is important to know the interrelationship of the absorption, distribution, binding, biotransformation, and excretion of a drug and its concentration at its locus of action.

E. Clinical Pharmacology and Therapeutics

1. Indications and Therapeutic Uses - Emphasis is placed on the therapeutic use of drugs for the treatment of disease in clinical pharmacology, internal medicine and therapeutics. There are specific clinic disorders or disease entities for which a given drug may be prescribed and the physician must weigh the potential benefit of drug use against the risks of adverse effects.

2. Contraindications and Factors (e.g., liver disease) May Modify Drug Action - where detoxification of the drug by the liver is important. It is important to know that the presence of disease or organ pathology may influence the actions of a drug. Conditions such as age, pregnancy, concomitant administration of other drugs and disease may alter the patient's response to a given drug.

3. Posology - Is an archaic term describing dosage regimens. Consideration of dosage schedules is a part of pharmacokinetics.

4. Bioavailability - The fraction of drug administered which is actually absorbed and reaches the systemic circulation following oral dosing. Preparations of the same drug by different manufacturers may have a different bioavailability.

5. Prescription writing - It is important that the physician write clear, error-free directions for the drug provider (pharmacist) and for the patient. Physicians must guard against prescribing too many drugs, or preparations of little value. Drugs of unproven clinical value should be avoided, as well as potentially toxic agents if drugs equally effective but less dangerous are available. Risk-benefit and cost-benefit should be considered. Drugs may be prescribed by generic name, since often a less expensive drug product can be obtained in this way. A

particular manufacturer may be specified if the physician has reason to believe a better or more reliable preparation is available from that manufacturer.

6. Drug Nomenclature - In addition to its formal chemical name, a new drug is usually assigned a code name by the pharmaceutical manufacturer. If the drug appears promising and the manufacturer wishes to place it on the market, a United States Adopted Name (USAN) is selected by the USAN Council which is sponsored by: 1) The American Medical Association 2) The American Pharmaceutical Association 3) The United States Pharmacopeial Convention

F. Toxicology –

That aspect of pharmacology that deals with the adverse effects of chemical agents. Toxicology is concerned not only with drugs used in therapy but also with the other chemicals that may be responsible for household, environmental or industrial intoxication.

1. Forensic Toxicology - Addresses medicolegal aspects of the use of chemicals that are harmful to animals or man. Analytical chemistry and fundamental toxicological principles are hybridized to underlie this aspect of toxicology. Nonetheless accidental poisoning with drugs is a health problem of major significance. More than 1/4 of the fatalities and about 1/2 of all poisonings occur in children under 5 years of age. All common household articles that are poisonous should be made unavailable to children, and poisonous rodenticides and insecticides should not be placed in the home.

2. Clinical Toxicology - Focuses on toxic events that are caused by or are uniquely associated with drugs or other chemicals.

G. Pharmacovigilance –

The area of pharmacology that focuses on the effects of drugs on patient safety. It involves the characterization, detection, and understanding of adverse events associated with drug administration, including adverse drug reactions, toxicities, and side effects that arise as a consequence of the short- or long-term use of drugs. Adverse drug reactions, including drug-drug interactions, are estimated to be a major cause of mortality of inpatients and also lead to significant increases in duration of hospitalization. No drug is free of toxic effects. Some untoward effects of drugs are trivial, but others are serious and may be fatal. Side effects often are predictable from a knowledge of the pharmacology of a particular drug. Examples of chemicals or drug-induced toxicities are given below:

1. Allergic reactions

2. Blood dyscrasias

3. Hepatotoxicity and nephrotoxicity

4. Teratogenic effects

5. Behavioral toxicity

6. Drug dependence and drug abuse

7. Carcinogenesis

8. Pharmacogenetic toxicities

ESSENTIAL DRUG CONCEPT-

The WHO has defined Essential Medicines (drugs) as “those that satisfy the priority healthcare needs of the population. They are selected with due regard to public health relevance, evidence on efficacy and safety, and comparative cost effectiveness. Essential medicines are intended to be available within the context of functioning health systems at all times and in adequate amounts, in appropriate dosage forms, with assured quality and adequate information, and at a price the individual and the community can afford It has been realized that only a handful of medicines out of the multitude available can meet the health care needs of majority of the people in any country, and that many well tested and cheaper medicines are equally (or more) efficacious and safe as their newer more expensive congeners.

The WHO has laid down criteria to guide selection of an essential medicine.

(a) Adequate data on its efficacy and safety should be available from clinical studies.

(b) It should be available in a form in which quality, including bioavailability, and stability on storage can be assured.

(c) Its choice should depend upon pattern of prevalent diseases; availability of facilities and trained personnel; financial resources; genetic, demographic and environmental factors.

(d) In case of two or more similar medicines, choice should be made on the basis of their relative efficacy, safety, quality, price and availability. Cost-benefit ratio should be a major consideration.

(e) Choice may also be influenced by comparative pharmacokinetic properties and local facilities for manufacture and storage.

(f) Most essential medicines should be single compounds. Fixed ratio combination products should be included only when dosage of each ingradient meets the requirements of a defined population group, and when the combination has a proven advantage in therapeutic effect, safety, adherence or in decreasing the emergence of drug resistance.

(g) Selection of essential medicines should be a continuous process which should take into account the changing priorities for public health action, epidemiological conditions as well as availability of better medicines/formulations and progress in pharmacological knowledge.

(h) Recently, it has been emphasized to select essential medicines based on rationally developed treatment guidelines.

ROUTES OF DRUG ADMINISTRATION

Local Routes

It is the simplest mode of administration of a drug at the site where the desired action is required. Systemic side effects are minimal.

1. Topical: Drug is applied to the skin or mucous membrane at various sites for local action.

a. Oral cavity: As a suspension, e.g. nystatin; as a troche, e.g. clotrimazole (for oral candidiasis); as a cream, e.g. acyclovir (for herpes labialis); as ointment and jelly, e.g. 5% lignocaine hydrochloride (for topical anaesthesia); as a spray, e.g. 10% lignocaine hydrochloride (for topical anaesthesia).

b. GI tract: As tablet that is not absorbed, e.g. neomycin (for sterilization of gut before surgery).

c. Rectum and anal canal: i. As an enema (administration of drug into the rectum in liquid form): – Evacuant enema (for evacuation of bowel): For example, soap water enema—soap acts as a lubricant and water stimulates the rectum. – Retention enema: For example, methylprednisolone in ulcerative colitis. ii. As a suppository (administration of the drug in a solid form into the rectum), e.g. bisacodyl— for evacuation of bowels.

d. Eye, ear and nose: As drops, ointments and sprays (for infection, allergic conditions, etc.), e.g. gentamicin eye/ear drops.

e. Bronchi: As inhalation, e.g. salbutamol, ipratropium bromide, etc. (for bronchial asthma and chronic obstructive pulmonary disease).

f. Skin: As ointment, cream, lotion or powder, e.g. clotrimazole (antifungal) for cutaneous candidiasis.

2. Intra-arterial route: This route is rarely employed. It is mainly used during diagnostic studies such as coronary angiography and for the administration of some anticancer drugs, e.g. for treatment of malignancy involving limbs.

3.Administration of the drug into some deep tissues by injection, e.g. administration of triamcinolone directly into the joint space in rheumatoid arthritis.

Systemic Routes

Drugs administered by this route enter blood and produce systemic effects.

Enteral Routes

It includes oral, sublingual and rectal routes.

Oral Route

It is the most common and acceptable route for drug administration. Dosage forms are tablet, capsule, syrup, mixture, etc., e.g., paracetamol tablet for fever, omeprazole capsule for peptic ulcer are given orally.

Advantages

Safer.

Cheaper.

Painless.

Convenient for repeated and prolonged use.

Can be self-administered.

Disadvantages

Not suitable for emergency as onset of action of orally administered drugs is slow.

It is not suitable for

Unpalatable and highly irritant drugs.

Unabsorbable drugs (e.g. aminoglycosides).

Drugs that are destroyed by digestive juices (e.g. insulin).

Drugs with extensive fi rst-pass metabolism (e.g. lignocaine).

Unconscious patients.

Uncooperative and unreliable patients.

Patients with severe vomiting and diarrhoea.

Sublingual Route

The preparation is kept under the tongue. The drug is absorbed through the buccal mucous membrane and enters the systemic circulation directly, e.g. nitroglycerin for acute anginal attack and buprenorphine for myocardial infarction.

Advantages

Quick onset of action.

Action can be terminated by spitting out the tablet.

Bypasses fi rst-pass metabolism.

Self-administration is possible.

Disadvantages

It is not suitable for: Irritant and lipid-insoluble drugs.

Drugs with bad smell and taste.

Rectal Route

Drugs can be given in the form of solid or liquid.

1. Suppository: It can be used for local (topical) effect as well as systemic effect, e.g. indomethacin for rheumatoid arthritis.

2. Enema: Retention enema can be used for local effect as well as systemic effect. The drug is absorbed through rectal mucous membrane and produces systemic effect, e.g. diazepam for status epilepticus in children.

Parenteral Routes

Routes of administration other than enteral route are called parenteral routes.

Advantages

Onset of action of drugs is faster; hence it is suitable for emergency.

Useful in: Unconscious patient.

Uncooperative and unreliable patients.

Patients with vomiting and diarrhoea

Disadvantages

Require aseptic conditions.

Preparations should be sterile and is expensive.

Requires invasive techniques that are painful.

Cannot be usually self-administered.

Can cause local tissue injury to nerves, vessels, etc.

Inhalation

Volatile liquids and gases are given by inhalation for systemic effects, e.g. general anaesthetics.

Advantages

Quick onset of action.

Dose required is very less, so systemic toxicity is minimized.

Amount of drug administered can be regulated.

Disadvantages

Local irritation may cause increased respiratory secretions and bronchospasm

AGONISTS

Receptors can be activated by either endogenous agonists (such as hormones and neurotransmitters) or exogenous agonists (such as drugs), resulting in a biological response. A physiological agonist is a substance that creates the same bodily responses but does not bind to the same receptor.

An endogenous agonist for a particular receptor is a compound naturally produced by the body that binds to and activates that receptor. For example, the endogenous agonist for serotonin receptors is serotonin, and the endogenous agonist for dopamine receptors is dopamine.

Full agonists bind to and activate a receptor with the maximum response that an agonist can elicit at the receptor. One example of a drug that can act as a full agonist is isoproterenol, which mimics the action of adrenaline at β adrenoreceptors. Another example is morphine, which mimics the actions of endorphins at μ-opioid receptors throughout the central nervous system. However, a drug can act as a full agonist in some tissues

and as a partial agonist in other tissues, depending upon the relative numbers of receptors and differences in receptor coupling.[medical citation needed]

A co-agonist works with other co-agonists to produce the desired effect together. NMDA receptor activation requires the binding of both glutamate, glycine and D-serine co-agonists. Calcium can also act as a co-agonist at the IP3 receptor.

A selective agonist is selective for a specific type of receptor. E.g. buspirone is a selective agonist for serotonin 5-HT1A.

Partial agonists (such as buspirone, aripiprazole, buprenorphine, or norclozapine) also bind and activate a given receptor, but have only partial efficacy at the receptor relative to a full agonist, even at maximal receptor occupancy. Agents like buprenorphine are used to treat opiate dependence for this reason, as they produce milder effects on the opioid receptor with lower dependence and abuse potential.

An inverse agonist is an agent that binds to the same receptor binding-site as an agonist for that receptor and inhibits the constitutive activity of the receptor. Inverse agonists exert the opposite pharmacological effect of a receptor agonist, not merely an absence of the agonist effect as seen with an antagonist. An example is the cannabinoid inverse agonist rimonabant.

ANTAGONISTS

An antagonist is a drug which blocks the response to an agonist e.g. Reserpine

Or

an **antagonist** is a drug that binds to the **receptor** either on the primary site, or on another site, which all together stops the **receptor** from producing a response.

Antagonism is the process of inhibiting or preventing an agonist-induced receptor response. Agents that produce this effect are called *antagonists*. The availability of selective antagonists has provided an important mechanistic tool. On the one hand, the classification of receptor subtypes was accomplished largely because of the availability of selective antagonists. Even with the proliferation of receptors resulting from molecular cloning, selective antagonists are an essential element of understanding the functional role of such receptors. Based on the kinetics of interaction of the antagonist with the receptor, antagonism is classified as *competitive* and *non-competitive*.

Competitive antagonism

Competitive antagonism is based on the principle that an agonist or antagonist can bind to the same recognition site(s) on the receptor, and when both agonist and antagonist are present concomitantly, they can compete for such sites. Reversible competitive antagonism occurs either when the binding of the antagonist can be eliminated by increasing the concentration of agonist, or when the antagonist dissociates as the free concentration decreases.

Nancompetitive Antagonism.

In this type of antagonism, the blockade of agonist response is produced by the interaction of the antagonist with binding sites intimately associated with the receptor, but distinct from the agonist binding site. It is assumed that the binding of the antagonist to this site precludes the activation of the receptor by the agonist. This could be conceptualized as if the noncompetitive antagonist removes the receptor, or eliminates the system's capacity to respond. Therefore, the maximal capacity of the receptor to respond is decreased due to a progressive decline in agonist fractional receptor occupancy. The agonist, however, operates normally at receptor-effector units not influenced by the antagonist. The affinity of the remaining receptors for the agonist, and the potency of the

SPARE RECEPTORS

Spare receptors, receptors may be considered spare when the maximal response is elicited by an agonist at a concentration that does not produce full occupancy of the available receptors.

• nickerson (1957) - histamine on a guinea pig ileum preparation
• furchgott (1964) - adrenaline induced contraction of the rabbit aortic strips
• only small percentage of receptors had to be occupied by agonist to produce maximum contraction(response)
• ‘spare’ or ‘reserve’ receptor • proposed by stephenson

Not all of the receptors in the tissue are required to achieve a maximal response.
Spare receptors exist when maximum drug response is achieved prior to saturation of all receptors, they are not hidden receptors, when they are occupied they can be coupled to response,widely misunderstood as non functional.
Spare receptor may be demonstrated by using irreversible antagonist. •experimentally, the spare receptor concept can be shown when the agonist can still produce an undiminished maximal response in presence of an irreversible antagonist.

ADDICTION

The term addiction does not only refer to dependence on substances such as heroin or cocaine. A person who cannot stop taking a particular drug or chemical has a substance dependence.

Some addictions also involve an inability to stop partaking in activities, such as gambling, eating, or working. In these circumstances, a person has a behavioral addiction.

When a person experiences addiction, they cannot control how they use a substance or partake in an activity, and they become dependent on it to cope with daily life.

Every year, addiction to alcohol, tobacco, illicit drugs, and prescription opioids costs the U.S. economy upward of $740 billion in treatment costs, lost work, and the effects of crime.

DRUG TOLERANCE

Drug tolerance is a pharmacological concept describing subjects' reduced reaction to a drug following its repeated use. Increasing its dosage may re-amplify the drug's effects; however, this may accelerate tolerance, further reducing the drug's effects. Drug tolerance is indicative of drug use but is not necessarily associated with drug dependence or addiction. The process of tolerance development is reversible (e.g., through a drug holiday) and can involve both physiological factors and psychological factors.
The opposite concept to drug tolerance is drug reverse tolerance (or drug sensitization), in which case the subject's reaction or effect will increase following its repeated use. The two notions are not incompatible and tolerance may sometimes lead to reverse tolerance

DRUG DEPENDENCE

Drug dependence is defined as a psychic and physical state of the person characterized by behavioral and other responses resulting in compulsions to take a drug, on a continuous or periodic basis in order to experience its psychic effect and at times to avoid the discomfort of its absence.

TACHYPHYLAXIS

Tachyphylaxis is a medical term describing an acute, sudden decrease in response to a drug after its administration;[1] i.e. a rapid and short-term onset of drug tolerance. It can occur after an initial dose or after a series of small doses. Increasing the dose of the drug may be able to restore the original response.

IDIOSYNCRASY

In pharmacology, idiosyncrasy refers to an idiosyncratic reaction, which is an adverse effect to an agent, such as a drug, which does not occur in most patients who've used the same agent.

That shouldn't be too surprising. In lay terms, when we say someone has a certain idiosyncrasy, we refer to a habit or mannerism that's peculiar to that person. Well, an idiosyncratic reaction is an abnormal event, stemming from the use of a compound, which is peculiar (specific) to an individual.

ALLERGY

An allergy is an immune system response to a foreign substance that’s not typically harmful to your body. These foreign substances are called allergens. They can include certain foods, pollen, or pet dander.

Your immune system's job is to keep you healthy by fighting harmful pathogens. It does this by attacking anything it thinks could put your body in danger. Depending on the allergen, this response may involve inflammation, sneezing, or a host of other symptoms.

Your immune system normally adjusts to your environment. For example, when your body encounters something like pet dander, it should realize it's harmless. In people with dander allergies, the immune system perceives it as an outside invader threatening the body and attacks it.