CHAPTER

Branches and Divisions of Pharmacology

1

Introduction

Pharmacology (*pharmakon*,"drug" in Modern Greek; and -*logia*, "study of") is the branch of medicine and biology concerned with the study of drug action.

Where a drug can be broadly defined as any man-made, natural, or endogenous (within the cell) molecule which exerts a biochemical and/or physiological effect on the cell, tissue, organ, or organism.

The two main areas of pharmacology are Pharmacodynamics and Pharmacokinetics. The former studies the effects of the drugs on biological systems, and the latter deals with the effects of biological systems on the drugs. In broad terms, pharmacodynamics discusses the actions of drugs with biological receptors and pharmacokinetics discusses the absorption, distribution, metabolism, and excretion of drugs from the biological systems.

Pharmacokinetics Vs. Pharmacodynamics

⇓	⇓
What the body does to the drug	What the drug does to the body

Dioscorides' De Materia Medica is often said to be the oldest and most valuable work in the history of pharmacology. The origins of clinical pharmacology date back to the middle ages in Avicenna's ***The Canon of Medicine*, Peter of Spain's *Commentary on Isaac*, and John of St Amand's *Commentary on the Antedotary of Nicholas*.** Clinical pharmacology owes much of its foundation to the work of William Withering. Pharmacology as a scientific discipline did not further advance until the mid-19th century amid the great biomedical resurgence of that period. Before the second half of the nineteenth century, the remarkable potency and specificity of the actions of drugs such as morphine, quinine and digitalis were explained vaguely and with reference to extraordinary chemical powers and affinities to certain organs or tissues. The first pharmacology department was set up by **Rudolf Buchheim** in 1847, in recognition of the need to understand how therapeutic drugs and poisons produced their effects.

Early pharmacologists focused on natural substances, mainly plant extracts. Pharmacology developed in the 19th century as a biomedical science that applied the principles of scientific experimentation to therapeutic contexts.

Drug

The word drug comes from a French word '*Drogue*' meaning a dry herb. It can be defined as:

Natural or synthetic substance which (when taken into a living body) affects its functioning or structure, and is used in the diagnosis, mitigation, treatment, or prevention of a disease or relief of discomfort in man or animals. According to WHO "Substance or material that is used or intended to be used to modify or explore physiological processes or pathological states, for the benefit of the recipient."

Drug Sources

1. **Plant sources:** Obtained from plant parts or products. Seeds, stems, roots, leaves, resins, and other parts yield these drugs. Examples include digoxin from digitalis and morphine from opium.
2. **Animal sources:** Glandular products from animals are used, such as insulin and thyroid.
3. **From micro-organisms (fungi, bacteria):** Penicillin was discovered by Alexander Fleming in 1928 as a product of *Penicillium notatum* (a mold growing in his lab).
4. **Mineral sources:** Some drugs are prepared from minerals, for example, lithium carbonate (an antipsychotic), $MgSO_4$ (Magnesium Sulphate) (a laxative).
5. **Synthetic sources:** Laboratories duplicate natural processes, and may modify the products. Frequently this can eliminate side effects and increase the potency of the drug. Examples include sulfonamides, and aspirin.
6. **Recombinant proteins:** Proteins that are synthesized by expression of cloned genes in recombinant cells, such as interferon's (INF 's), antibodies.
7. **Hybridoma technique:** E.g., monoclonal antibodies (MAB).

Drug Nomenclature

Chemical name: Represents the exact description of the drug's chemical composition.

Generic name (non-proprietary) : Simpler than the chemical name and derived from the chemical name itself. Easier to remember.

***Example* 1:** The chemical name 2-methyl-5-nitroimidazole-1-ethanol is metronidazole. The word methylnitro is condensed to metro and nidazole is due to its imidazole ring.

***Example* 2:** Metoclopramide is the condensed form of the word methoxychloroprocainamide: where Me is retained and th is written as t; chloro is written as clo: and procainamide is written as pramide.

Brand or trade name (proprietary): It is developed by the company requesting approval for the drug and identifies it as the exclusive property of that company.

***Example* 1:** Metrogyl® is the trade name for Metronidazole.

***Example* 2:** Reglan® is the trade name for Metoclopramide.

***Example* 3:** Amoxil® is the trade name for Amoxycillin.

***Example* 4:** Celebrex® is the trade name for Celecoxib.

The Nature of Drugs

A. Size: The great majority of drugs lie in the range from molecular weight 100 to 1,000. Drugs in this range are large enough to allow selectivity of action and small enough to allow adequate movement i.e., permeability within the various compartments in the body (Fig. 1-1).

B. Chemistry and reactivity: Drugs may be small, simple molecules (amino acids, simple amines, organic acids, alcohols, esters, ions, etc.), carbohydrates, lipids, or even proteins. Binding of drugs to their **receptors** the specific molecules in a biologic system that mediate drug effects, is usually by noncovalent bonds (hydrogen bonds, van der Walls attractions, and ionic bonds), and less commonly by covalent bonds. Weaker, noncovalent bonds require a better fit of the drug to the receptor binding site and, usually, a reversible type of action. Very strong bonding, e.g., covalent bonds, usually involves less selectivity and an irreversible interaction.

C. Shape: The overall shape of a drug molecule is important for the fit of the drug to its receptor. Between a quarter and a half of all drugs in use exist as stereoisomers. In most cases the stereoisomers are chiral **Enantiomers**. Enantiomers are mirrored image twin molecules that result from the presence of an asymmetric carbon, or in a few cases, other asymmetric atoms in their

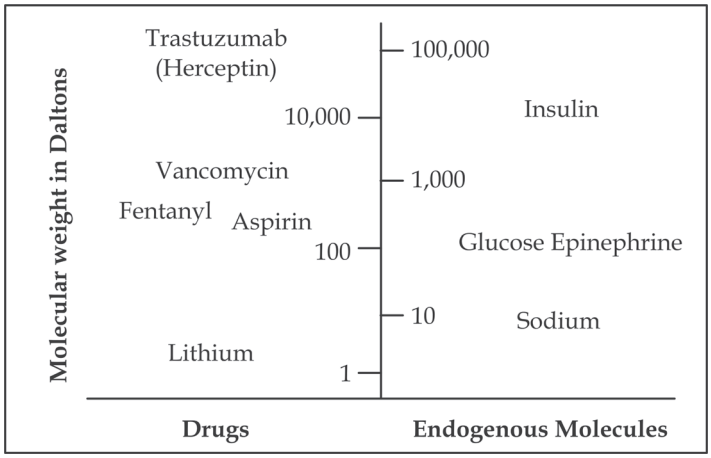


Fig 1-1: Molecular weights of several endogenous molecules and drugs. Lithium is used to treat people with psychiatric disorders, fentanyl is an opioid analgesic and *trastuzumab* is an antibody used to treat women with breast cancer.

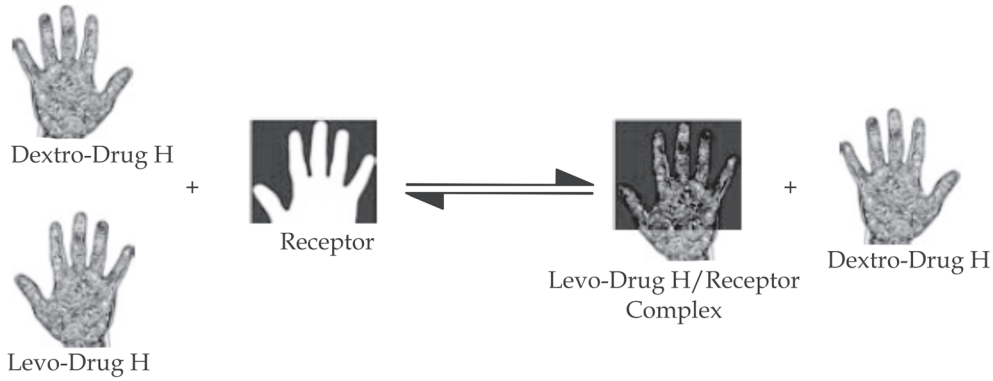


Fig 1-2: The two hands represent the enantiomer of Drug H. The shape of the Levo enantiomer allows it to bind tightly to the drug-binding site in the receptor.
Note: that this binding is reversible.

structures. Here drug action is based on the rotation of drug molecule, (Fig. 1-2) for example : Levo cetrizine and cetrizine actions for allergic reactions. Chiral enantiomers often differ in their ability to bind to and alter the function of receptors. They also can differ in their rates of elimination and in their toxicity. Most chiral drugs are still provided as **racemic mixtures** (mixtures of isomers) because it is expensive to separate the stereoisomers. In the past, little was known about the relative activity of stereoisomers. However, the Food and Drug Administration (FDA) now requires information about the structure and activity of each isomer present in a racemic mixture of a new medication.

Branches of Pharmacology

Following are the important branches of Pharmacology:

1. Pharmacokinetics
2. Pharmacodynamics
3. Pharmacotherapeutics
4. Chemotherapy
5. Toxicology

6. Clinical pharmacology
7. Pharmacy
8. Pharmacognosy
9. Pharmacoeconomics
10. Pharmacogenetics
11. Pharmacogenomics
12. Pharmacoepidemiology
13. Comparative Pharmacology
14. Posology
15. Animal Pharmacology
16. Behavioural pharmacology
17. Environmental pharmacology
18. Neuropharmacology
19. Psychopharmacology

1. ***Pharmacokinetics:*** The word Pharmacokinetics is derived from two words, pharmacon meaning "drug" and kinetics meaning "putting in motion". It can be defined as:
   "The branch of pharmacology that deals with the absorption, distribution, metabolism and excretion of drugs and their relationship with the onset, duration and intensity of the drug effect". What the body does to the drug is pharmacokinetics.
2. ***Pharmacodynamics:*** Pharmacodynamics is the branch of pharmacology that deals with the mechanism of action of drug and the relation between the drug concentration and its effect, study of physical and chemical effects of drugs on body, parasites and microorganisms. What the drug does to the body is pharmacodynamics. For example, adrenaline acts on adrenal receptors, stimulates adenyl cyclase system producing effects such as cardiac stimulation and hyperglycemia was studied in pharmacodynamics.
3. ***Pharmacotherapeutics:*** The branch of pharmacology that deals with the art and science of treatment of disease. It is the application of pharmacological information together with the knowledge of disease, for the prevention and cure of the disease.
4. ***Chemotherapy:*** Chemotherapy refers to the treatment of diseases by chemicals that kill the cells, especially those of microorganisms and neoplastic cells. It is classified into two divisions:

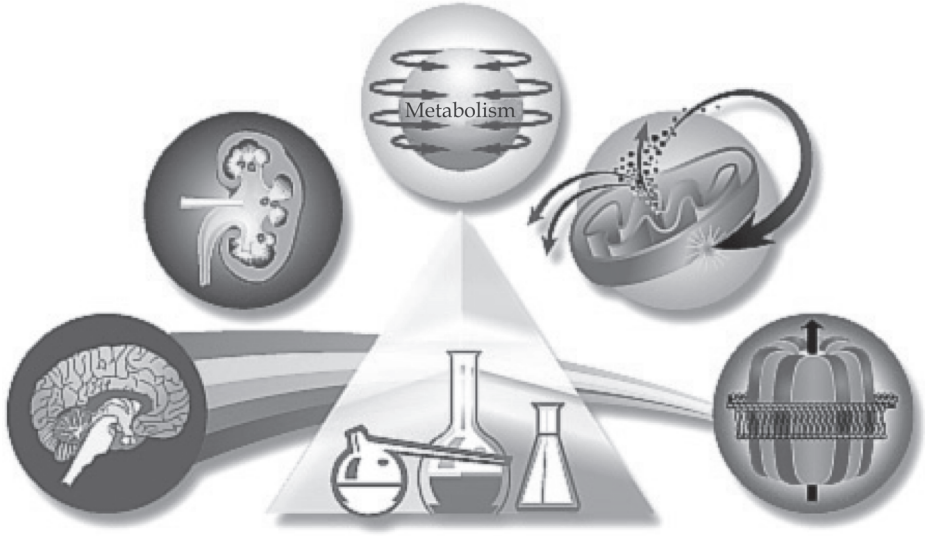


Fig 1-3: A variety of topics involved with pharmacology, including neuropharmacology, renal pharmacology, human metabolism, intracellular metabolism, and intracellular regulation.

(a) *Antibiotics:* Includes the choice of drugs most potent against the organism or least toxic. Examples include Erythromycin given for gram positive organisms and Aminoglycosides for gram negative organisms.

(b) *Antineoplastics*

Examples include:

Methotrexate, which is anticancer drug. It inhibits the dihydrofolate reductase and interferes with the DNA synthesis and repair.

Vinca alkaloids, which bind tubulin of microtubules and arrest mitosis in metaphase.

5. ***Toxicology:*** Toxicology is the branch of pharmacology which includes the study of adverse effects of drugs on the body. It deals with the symptoms, mechanisms, treatment and detection of poisoning caused by different chemical substances.

   The main criterion is the dose. Essential medicines are poisons in high doses and some poisons are essential medicines in low doses.

6. ***Clinical pharmacology:*** Clinical pharmacology is the scientific study of drugs in man. It includes pharmacokinetic and pharmacodynamic investigations in healthy or diseased individuals. It also includes the comparison with placebos, drugs in the market and surveillance programmes.

   The main objectives are:

   1. Maximize the effect of drug
   2. Minimize the adverse effects
   3. Promote safety of prescription

   Aims include:

   1. Generate optimum data for use of drug.
   2. Promote usage of evidence based medicine.

7. ***Pharmacy:*** Pharmacy is the branch of pharmacology and is the art and science of compounding by dispensing drugs, preparing suitable dosage form for administration to man and animals. The health profession blends health science with chemical science and effective use of drugs.

8. ***Pharmacognosy:*** Pharmacognosy is the identification of drugs by just seeing or smelling them. It is a crude method no longer used. Basically it deals with the drugs in crude or unprepared form and study of properties of drugs from natural sources or identification of new drugs obtained from natural sources.

9. ***Pharmacoeconomics:*** Pharmacoeconomics deals with the cost of drugs. In this discipline the cost of one drug is compared with another for same use. The cheap drugs are preferred.

10. ***Pharmacogenetics:*** Branch of pharmacology dealing with the genetic variations that cause difference in drug response among individuals or population. Example includes succinyl choline which is a skeletal muscle relaxant used in general anaesthesia. It is metabolized by pseudocholine esterase and has short duration of action. The presence of enzyme is determined by the gene and lack of this is recessively inherited. This may lead to respiratory paralysis, apnea and death.

11. ***Pharmacogenomics:*** Pharmacogenomics is the broader application of genomic technologies to new drug discovery and further characterization of older drugs.

    Recombinant DNA technology involves the artificial joining of DNA of one species to another. *E. coli* is mostly used. In this way we can get huge amounts of drug in purified form which is less antigenic.

    Examples include GH (Growth Hormone), inter interferon and vaccines.

12. ***Pharmacoepidemiology:*** Pharmacoepidemiology deals with the effects of drugs on a large population. The effects may be good or harmful. It is conducted in three ways:

    (a) Observational cohort studies
    (b) Case control studies
    (c) Phase trials

    (a) *Observational cohort studies:* Patients receiving drugs are collected and followed up to determine the outcomes. It is prospective (forward looking) research, however, is time consuming and lengthy.

(b) *Case control studies:* These are retrospective studies. They reverse the direction of scientific logic from forward looking to backward looking.

(c) *Phase trials:* These include different phases: (Fig. 1-4).

13. ***Comparative pharmacology:*** Branch of pharmacology dealing with the comparison of one drug to another belonging to the same or another group.

14. ***Posology:*** Posology deals with the dosage of drugs. Example includes paracetamol given as one tablet of 500 mg thrice a day for an adult.

15. ***Animal pharmacology:*** Animal pharmacology deals with the different properties of drugs in animals. A vast variety of animals are utilized including rabbits, mice guinea pigs, etc. Drugs are given to the animals and all parameters (their behaviour, activities, vital signs, physiological and anatomical changes etc.) are recorded. Any change is noted down. If any change was found to be useful in animals, then the drug is tested on humans.

16. ***Behavioural pharmacology:*** Behavioural pharmacology, also referred to as psychopharmacology, is an interdisciplinary field which studies about behavioural effects of psychoactive drugs. It incorporates approaches and techniques from neuropharmacology, animal behaviour and behavioural neuroscience, and is interested in the behavioural and neurobiological mechanisms of action of psychoactive drugs. Another goal of behavioural pharmacology is to develop animal behavioural models to screen chemical compounds with therapeutic potentials. People in this field (called behavioural pharmacologists) typically use small animals (e.g., rodents) to study

Phases of Clinical Drug Development

	I	IIa	IIb	III	FDA	IV
Subjects	Healthy Normals	**First** time in Patients	Patients	Patients		Patients
Number	20 – 100	20 – 75	50 – 200	> 300		> 1,000
Measures	Asc. Dose, Kinetics, Equivalence, Safety	Dose range MOA, Efficacy, Safety	Efficacy, Safety	Efficacy, Safety		Efficacy, Safety, New uses
Value	Kinetics, Dynamics	**Proof of Concept**	Confirm mechanism of action	Confirm usefulness	Review Approve or disapprove	Surveillance, extend patent expand market
Where	In-House (controlled)	In-House (controlled)	Ambulatory	Ambulatory		Ambulatory
Time (Years)	1 – 1.5	1	1 – 1.5	3 – 6	2 – 3	1 – 2

Fig 1-4: Phases of clinical drug development

psychotherapeutic drugs such as antipsychotics, antidepressants and anxiolytics, and drugs of abuse such as nicotine, cocaine, methamphetamine, etc.

17. ***Environmental pharmacology:*** Environmental pharmacology is a new discipline. Focus is being given to understand gene-environment interaction, drug-environment interaction and toxin-environment interaction. There is a close collaboration between environmental science and medicine in addressing these issues, as healthcare itself can be a cause of environmental damage or remediation. Human health and ecology is intimately related. Demand for more pharmaceutical products may place the public at risk through the destruction of species. The entry of chemicals and drugs into the aquatic ecosystem is a more serious concern today. In addition, the production of some illegal drugs pollutes drinking water supply by releasing carcinogens.
18. ***Neuropharmacology:*** Effects of medication on central and peripheral nervous system functioning.
19. ***Psychopharmacology:*** Effects of medication on the psycho; observing changed behaviours of the body and mind, and how molecular events manifest in a measurable behavioural form.

Hypersensitivity

Hypersensitivity (or allergy) is an exaggerated response of the immune system to antigen challenge, harmful to the organism itself. Although the basic phenomenology of most types of hypersensitivity reactions was established at the end of the 19th century and in the early years of the 20th century (Koch's phenomenon, Richet and Portier's anaphylaxis, Arthus's phenomenon and serum sickness), it was only in 1963 that **Patrick Gell and Robin Coombs** produced a comprehensive classification of hypersensitivity reactions according to their underlying immune effector mechanism.

The Gell and Coombs classification distinguishes four types of reactions based on antibody (I-III) or cell-mediated (IV) effector mechanisms. Since the original classification, our understanding of the molecular and cellular immune reactions has considerably developed and several number of attempts have been made to revise or re-interpet the Gell and Coombs scheme but, to this time, the Gell and Coombs classification remains the most valid and useful frame work for understanding hypersensitivity.

There is a significant difference between Type I hypersensitivity and the other types of hypersensitivity caused by antibodies (Type II and III), namely the fact that Type I reactions occur only in a proportion of the subjects exposed to the agent in question (atopic individuals). Type II and III reactions, instead, occur in all individuals. For example, haemolytic transfusion reactions (HTR) occur whenever a blood transfusion between ABO incompatible individuals is carried out, the haemolytic disease of the newborn occurs whenever a Rh- mother produce an antibody response to Rh+, foetal RBC and serum sickness occurs whenever repeated and substantial doses of foreign serum is injected in patients for therapeutic purposes, as it occurred in the early days of serotherapy (Injections of a serum obtained especially from an immune animal). The common feature of Type I, II and III is that in all cases the antibody reactions induce cell or tissue damage (hence it appears justified that Gell and Coombs define all these reactions Hypersensitivity) but in the majority of Type II and III reactions there is no individual susceptibility or exaggerated response and, in the case of the HTR due to ABO incompatibility, there is not even a first sensitisation phase.

Type I Hypersensitivity

Antigens causing Type I hypersensitivity reactions (or **immediate-type hyper-sensitivity**) are defined as **allergens** and induce the formation of antibodies of the IgE isotype in certain individuals. IgE-based antibody responses are common physiologically in parasitic infections but **atopic**

individuals produce IgE responses against a number of non-parasitic antigens that induce either no antibody response or antibody response of a different isotype, typically IgG, in normal individuals. Atopic individuals thus are susceptible to either generalised anaphylaxis local tissue reactions that involve a similar pathogenetic mechanism, namely asthma, hay fever, eczema or food allergies.

The tissue response caused by type I hypersensitivity reactions is now well understood and is determined by the binding of IgE antibodies to a high affinity receptor which binds the Fc portion of IgEs with subnanomolar affinity and located on the membrane of mast cells and basophils. As a result, a significant fraction of the IgE produced following initial contact with antigen, becomes 'fixed' on the surface of these cells and, in case of a second contact with antigen, the antigen-antibody reactions occurs not only in solution but also or predominantly on the mast cell and basophil membrane .

The IgE-antigen reaction occurring on the surface of basophils and mast cells leads to receptor cross-linking and **degranulation**, i.e., release of vasoactive amines (histamine and serotonin) and other agents (heparin, eosinophil and neutrophil chemotactic factors, platelet-activating factor, a variety of cytokines and prostaglandins and leukotrienes) from the cytoplasmic granules, which collectively cause contraction of smooth muscle cells, vasodilation, increased vascular permeability and platelet aggregation and degranulation. These reactions can affect a single tissue or organ (as in asthma, hay fever or eczema) or multiple ones (as in generalised anaphylaxis) depending on local or general re-exposure to the allergen.

Type II Hypersensitivity

Unlike Type I reactions, Type II hypersensitivity is caused by direct antibody-mediated cell damage or lysis. The actual mechanisms underlying cell destruction are multiple (*Type II hypersensitivity - antibody-dependent cytotoxicity)*:

(i) Complement-dependent red blood cell lysis, for example, as a result of haemolytic transfusion reactions (HTR) caused by ABO incompatibility and in other forms of haemolytic anaemias.

(ii) Antibody-dependent red blood cell degradation occurs, for example, as the result of binding of antibodies to the red cell membrane which fail to activate complement but promote macrophage uptake and RBC degradation. This occurs for example, in the haemolytic disease of the newborn (HDN) caused by Rh incompatibility.

(iii) Antibody-dependent cell-mediated cytotoxicity (ADCC), which occurs when cytotoxic antibodies become fixed on the surface of cytotoxic T cells and subsequent antigen binding induce perforin-dependent cell lysis of the cell bearing the antigen.

Type III Hypersensitivity

Type III hypersensitivity reactions are caused by antibody-antigen complexes. When significant quantities of such immune complexes are formed, they can deposit in tissues and lead to a tissue reaction which is initiated by complement activation and leads to mast cell degranulation, leukocyte, predominantly neutrophil, chemotaxis and an inflammatory reactions caused by the activation of these cells.

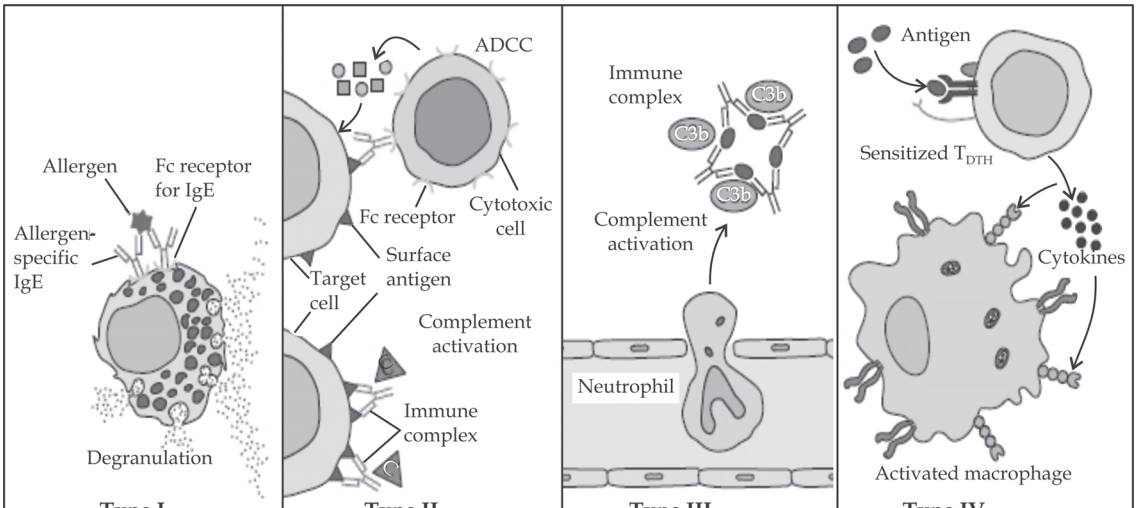
There are systemic forms of type III hypersensitivity reactions, such as serum sickness, a disease which is now of pure historic interest but was a common occurrence in patients receiving repeated injections of anti-diphtheric horse serum and in which immune complex deposition occurred in a variety of tissues and organs leading to fever, generalised vasculitis with edema and erythema, arthritis and glomerulonephritis.

There are also local forms of immune complex diseases, such as the Arthus phenomenon . In both systemic and local forms of Type III hypersensitivity reactions, the emergence as well as the resolution of the tissue

lesions and clinical symptoms follow strictly the formation of the immune complexes, the cause of tissue damage (see Fig 1-5). The principal mechanism responsible for tissue damage as a result of deposition of immune complexes is mediated by complement components, mainly the C3a and C5a anaphylotoxins, that attract phagocytes and mast cells and, following binding to complement receptors on the surface of such cells, lead to degranulation causing a local inflammatory reaction (vasodilation, increased vascular permeability, etc.)

Type IV Hypersensitivity

The prototypical Type IV (or delayed-type hypersensitivity, DTH) tissue reaction is Koch's phenomenon. Type IV hypersensitivity reactions are caused by activated TH_1 cells that are activated by intracellular pathogens, including bacteria, fungi and protozoa, as well certain chemicals (hair dyes, nickel salts) leading to clonal expansion and differentiation of antigen-specific cells into TH_1 clones. This corresponds to the sensitisation phase of DTH.



Type I	Type II	Type III	Type IV
IgE-Medicated Hypersensitivity	IgE-Medicated Cytotoxic Hypersensitivity	Immune Complex-Mediated Hypersensitivity	Cell-Mediated Hypersensitivity
Ag induced crosslinking of IgE bound to mast cells and basophils with release of vasoactive mediators	Ab directed against cell surface antigens meditates cell destruction via complement activation or ADCC	Ag-Ab complexes deposited in various tissues induce complement activation and an ensuing inflammatory response mediated by massive infiltrtation of neutrphils	Sensitized T_H1 cells release cytokines that activate macrophages or T_c cells which mediate direct cellular damage
Typical manifestations include systemic anaphylaxis and localized anaphylaxis such as hay fever, asthma, hives, food allergies, and eczema	Typical manifestations include blood transfusion reactions, erythroblastosis fetalis, and autoimmune hemolytic anemia	Typical manifestations include localized Arthus reaction and generalized reactions such as serum sickness, necrotizing vasculitis, glomerulnephritis, rheumatoid arthritis, and systemic lupus erythematosus	Typical manifestations include contact dermatitis, tubercular lesions and graft rejection

Fig 1-5: Types of hypersensitivity reactions

Upon re-encounter with antigen, in the so-called effector phase, the antigen-specific TH_1 clones undergo further clonal expansion and secretion of a variety of effector molecules. These include both cytokines (such as IFN-gamma, TNF-beta, IL-2 and IL-3) and chemokines such as IL-8, Monocyte chemotactic and activating factor (MCAF) and a migration inhibiting factor (MIF) that collectively lead to macrophage activation and to the development of a local tissue reaction.

Thus DTH is ultimately mediated by the macrophages recruited and activated by the products of antigen-specific TH_1 clones. Unlike Type I, II and III reactions that can be transferred by serum (i.e., serum antibodies), passive transfer of type IV requires the transfer of antigen-specific TH_1 clones that orchestrate the macrophage response.

Drug Response and Factors Affecting Drug Response

Variations in the response to the same dose of a drug between different patients and even in the same patient on different occasions have been observed. The range of variability is more marked with drugs disposed by metabolism than with drugs excreted unchanged in urine. The dose of drug is generally expressed in the range, which gives therapeutic effect in majority of patients. The dose range usually based on the average requirements of an adult and is not strictly applicable under all circumstances.

Important Factors Modifying Drug Action are:

- Body Weight/Size
- Age
- Sex
- Environmental factors
- Route of drug administration
- Time of drug administration
- Emotional factors
- Genetic factors
- Pathological states or presence of disease
- Metabolic disturbances
- Cumulative effect of drugs
- Other drug therapy
- Additive effect or summation
- Synergism
- Potentiation
- Tachyphylaxis/desensitization
- Tolerance
- Antagonism

Body weight/size: Obese (overweight) patients may require more medication than thin patients because of the drug has more tissue to which it can go. The dosage of many drugs is calculated on a weight basis. For example, a person might be prescribed a drug that has a dosage of 5 milligrams of drug per pound of patient body weight i.e., 5 mg × 5 pounds = 25 mg.

Age: As a rule, the very young and the elderly require less than the normal adult dose of most medications. Part of this requirement for less medication is due to the altered metabolism of the drug. Since body enzyme systems greatly influence drug metabolism, considering the differences in these enzyme systems based upon age is important especially CYP Enzyme. In the infant, some enzyme systems are not yet fully developed. On the other hand, the enzyme systems of the elderly may not function as well as in the past. Although several formulas are available for calculating a child's dose of medication, the two most accepted methods are those based upon the patient's weight (that is, milligrams per kilogram of body weight) or body surface area (that is, milligrams per square meter of surface area). Many examples of age-related differences in the response of individuals to a particular drug have been documented. In many cases these differences can be related to modified distribution, metabolism or excretion of the drug. There is evidence that in neonates and the elderly, the extent and rate of these processes are less than those in older children and young adults.

Anatomical changes: Age-related changes in the kidneys, liver, and other organs will influence the way many medications work. Nutritional status, multiple chronic diseases, and functional and cognitive deficits are other age-related factors that may have an impact on drug therapy. In general, because of a loss of muscle mass, elderly persons are physically smaller than younger adults. In addition, the percentage of body fat increases, and body water decreases. Cardiac output (the amount of blood that the heart pumps in one minute) decreases in most elderly persons as well. Kidney function gradually declines, and the effectiveness of the immune system decreases. These changes require a decrease in the dose of some medications to optimize their benefits and avoid toxicity and adverse reactions.

Physiologic changes: Physiologic changes that normally occur with aging may affect the way drugs work within the body. However, in a given age group there is no consistent trend for all drugs. In some cases the increased plasma concentration of the drug would be regarded as an advantage as it prolongs the response, but it is certainly not true for drugs such as streptomycin, warfarin and the hypoglycemic agents. Two points which emerge from the results of many studies with neonates and the elderly are that interindividual variations in plasma half-lives, metabolite and drug excretion and protein binding are significantly larger than those in young adults and that in the case of the elderly, chronological age does not necessarily reflect biological age. In combination these factors emphasise the importance of individual drug monitoring of plasma levels and hence of knowing the pharmacokinetic constants of the drug in the individual patient. In clinical practice, the dose of a drug is most commonly calculated on the basis of body weight or surface area. This is generally perfectly acceptable for older children and adults, but is not always a reliable formula for neonates and the very old. Simple changes in such parameters as urine pH can override calculations based upon body size.

Sex: Physiological differences between the sexes may influence the dose or the requirement for drugs. Since females have proportionately more fat tissue than males, drugs, which have a high affinity (likeness) for fat, may require larger doses in females. Moreover, estrogen and testosterone, two sex hormones, can affect the patient's rate of metabolism which can, in turn, influence the rate at which a drug is absorbed, metabolized, or excreted from the body. The requirement for iron is much higher in the female than in the male, because of the loss of blood in each menstural cycle. In women consideration must be given to mensturation, pregnancy and lactation. Drugs given during pregnancy may affect the fetus. Marked physiological changes occur during pregnancy that can alter the drug disposition. For example, G.I.T motility is decreased that results in delayed absorption of drug, plasma protein concentration and consequently binding of drug to proteins is increased during pregnancy, enzyme induction is observed and renal blood flow increases that cause rapid elimination of drug. The overall effect on drug disposition is complex and difficult to predict; drugs should be carefully given during pregnancy. A number of drugs like clonidine, methyldopa, and α-blockers interfere with sexual function in males but not in females. Gynecomastia produced by drugs like Digitalis, Cimetidine, Ketoconazole, Metoclopramide, Spironolactone and Chlorpromazine occur in males not in females.

Environmental factors: Drug metabolism is slow at high altitude due to oxygen deficiency. Cigarette smokers and industrial workers exposed to some pesticides metabolize drugs rapidly due to enzyme induction. Metabolism is low in hot and humid climate. Purgatives act better in summer while diuretics act better in winters. Oxidation of drugs is low at higher altitudes.

Route drug of Administration: Some drugs are incompletely absorbed after oral intake, when given intravenously; their dose has to be reduced. Examples include morphine and magnesium sulphate. Magnesium sulphate when given orally is osmotic purgative, but its 20% solution

is injected intravenously to control the convulsions in eclampsia of pregnancy. Aminoglycosides like streptomycin when given intravenously cause neuromuscular blockage, which is not observed after intramuscular injection.

Time of drug Administration: Hypnotics (producing sleep) act better when administered at night and smaller doses are required. There is delayed drug absorption when drug is given orally after meals, which slows down the effects of drug. Drugs are usually given after meals to prevent gastric irritation. Under certain circumstances drugs must be given before meals.

To prevent mixing of drug with food: Anthelmintics.

To get immediate effect: Drugs used for prevention of motion sickness.

To prevent formation of insoluble complexes: Tetracyclines.

To prevent specific side effects, for example, to prevent hypoglycemia, insulin and sulfonylureas are given before meals.

Emotional factors: Personality of physician and patient may influence the effects of drug. Sometimes inert dosage forms can relieve the symptoms this is called "PLACEBO". Placebo resembles the actual medicine in physical characteristics; it works by psychological rather than pharmacological effects and often produces response equivalent to the actual drug. Placebo is used to compare the therapeutic effects of various drugs during therapeutic trials of the drugs. Personality of patient also affects the drug response, nervous and anxious patients require more general anesthetics than normal persons do. Word placebo means "I SHALL PLEASE". Placebo resembles the actual medicine in physical characteristics. Placebo can be given orally as well as parenterally. It does not produce drug – drug interactions. Substances used as placebo are lactose, distilled water and dextrose.

Genetic factors: Genetic abnormalities influence the dose of a drug and response to drugs. It affects the drug response in individuals at 2 levels. At the level of receptors and at the level of drugs metabolizing enzyme. Thus, interfering with the functions such as rate of plasma drug clearance. Pharmacogenetics is the study of the relationship between genetic factors and drug response. Idiosyncrasy is the abnormal drug reaction due to genetic disorder. It is the unpredictable response seen on first dose of drug on hereditary basis. This may be due to Acetylation, Oxidation, Succinylcholine apnea and Glucose 6-phosphate dehydrogenase deficiency.

All individuals do not respond in similar way to same drug. Idiosyncrasy is used to describe abnormal drug response on administration of first dose.

Genetic polymorphism: The existence in a population of two or more phenotypes with respect to the effect of a drug. E.g., Acetylation enzymes deficiency-Acetyl transferase (non-microsomal) affects isoniazid, sulphonamides, etc.

Slow acetylator phenotype may show peripheral neuropathy.

Rapid acetylator phenotype may show hepatitis.

Pseudocholinesterase deficiency: Succinyl choline is a skeletal muscle relaxant. Succinylcholine apnea may occur due to paralysis of respiratory muscles.

Malignant hyperthermia: Occurs by succinyl choline due to inherited inabilityto chelate calcium by sarcoplasmic reticulum resulting in Ca^{+2} release, muscle spasm and rise in temperature.

Oxidation polymorphism: In case of Debrisoquine.

Extensive metabolizers (EM) - need larger dose.

Poor metabolizers (PM) – need smaller dose.

Deficiency of Glucose-6 phosphate dehydrogenase (G-6-PD): G-6-PD Deficiency in RBCs leads to haemolytic anaemia upon exposure to some oxidizing agents like

Antimalarial drug, primaquine

Long acting sulphonamides

Fava beans (favism)

Pathological states/ Presence of disease: Diseases cause individual variation in drug response.

In liver diseases, prolonged duration of action occurs because of increased half life. Plasma protein binding for warfarin, tolbutamide is decreased leading to adverse effects, If hepatic blood flow is reduced; clearance of morphine, propranolol may be affected. Impaired liver microsomal enzymes may lead to toxic levels of diazepam, rifampicin and theophylline.

In renal disease GFR, tubular function and plasma albumin may be affected leading to abnormal effects of digoxin, lithium, gentamycin and penicillin. In **Malnutrition** plasma protein binding of drugs is reduced along with the amount of microsomal enzymes, leading to increased portion of free, unbound drug e.g., warfarin

Metabolic disturbances: Changes in water and electrolyte balance, body temperature and acid base balance may modify the effects of drug. For example, aspirin reduces body temperature only in presence of fever and have no effect on body temperature when it is normal. Iron is well absorbed in states of iron deficiency. Vasoconstrictor effect of norepinephrine is reduced in presence of metabolic acidosis.

Cumulative effect of drugs: Cumulative effect of drugs is

1. Due to many frequent doses.
2. Due to prolonged continued administration.

By cumulative effect is meant the unexpected, intense action of a drug after it has been given for some time, as differing from an immediate intense action of a drug which would show an idiosyncrasy.

1. The too frequent administration of a drug which is slow of excretion will cause it to accumulate and sooner or later produce a poisonous effect. Therefore, "the duration of the action of a drug", it is very important to remember how long it ordinarily takes a given drug to be excreted. For instance, if a drug that is excreted in eight hours was administered every two hours, at the end of eight hours five doses will have been taken, only the first of which has been completely excreted, leaving three doses acting and one beginning to act in the system.
2. Cumulative action from too long continued administration of a drug means the development of symptoms which show an over-action of the drug. This is of frequent occurrence and is sometimes accidental, but is often caused deliberately by pushing a drug to its full physiologic effect. In cases in which this action occurs unexpectedly and is undesired, the drug should be immediately stopped, and not again given in doses that could cause such an effect. Some drugs give notice of such an impending action by premonitory symptoms; such is true of digitalis.

In some diseases such cumulative physiologic action of certain drugs is desired. The drug is then stopped temporarily, and then again pushed to the point of tolerance, the best way to combat such over-action, and which drugs will produce an over-action without danger to the patient, can be learned only by the study of the pharmacology of the drugs.

Other drug therapy: Drugs may modify the response to each other by pharmacokinetic or pharmacodynamics interaction between them. Drug interaction does not necessarily mean that their concurrent use is contraindicated; many drugs can be used beneficially with dosing schedule adjustment.

Additive effect or Summation: When total pharmacological effect produced by concomitant use of two or more drugs is equal to the sum of their individual effects, it is called "Additive effect".

$$1 + 1 = 2$$

Example: Combination of ephedrine and theophylline in the treatment of asthma. The individual side effects of an additive pair may be different, and may not add up. The combination is better tolerated than higher dose of one component.

Aspirin + paracetamol as analgesic/ antipyretic

Nitrous oxide + ether as general anaesthetic

Antihypertensive drugs

Cardiac stimulants

Synergism: When total pharmacological effect produced by concomitant use of two or more drugs is higher than the sum of their individual effects, it is called "Synergism".

$$1 + 1 = > 2.$$

Example: Codeine + Aspirin > Analgesia

Sulphonamide + Trimethoprim > Antibacterial effect

Potentiation: Enhancement of effect of one agent by another; so that the combined effect is more than the sum of their individual effects is called "Potentiation." In case of potentiation one agent has no effect when give alone but increases the effects of other co-administered drug.

$$0 + 1 \geq 2$$

Example: Acetylcholine + physostigmine. Physostigmine inhibits the action of esterase prolonging the effect of acetylcholine.

Levodopa (Parkinsonism) + carbidopa/ benserazide. Levo/dopa is decarboxylated peripherally, carbidopa inhibits the decarboxylase.

Sulphonamide (effective against some microorganisms) when combined with trimethoprim is effective against a wider range of microorganisms.

Levodopa + Carbidopa = Parkinsonism.

Ampicillin + Clavulanic acid = ≥ Antibacterial effect.

The action is more than the normal therapeutic effect.

Tachyphylaxis and Desensitization: Repeated administration of a drug at short intervals of time leads to decrease in pharmacological response. Desensitization and tachyphylaxis are synonymous terms used to describe this phenomenon which often develops in course of few minutes. This occurs with indirectly acting drugs like amphetamine, ephedrine, MDMA (3,4-methylenedioxy-N-methylamphetamine). On repeated administration, depletion of endogenous receptors occurs. It is also known as acute tolerance. Example includes ephedrine, which acts by releasing noradrenaline from adrenergic stores. After repeated administration, these stores are exhausted and pharmacological action is not restored even on increasing the dose.

Characteristics: Tachyphylaxis is characterized by the rate sensitivity: The response of the system depends on the rate with which a stimulus is presented. To be specific, a high-intensity prolonged stimulus or often-repeated stimulus may bring about a diminished response also known as desensitization. (Fig. 1-6)

Molecular interaction: In biological sciences, molecular interactions are the physical basis of the operation system. The control of the operation, in general, involves interaction of a stimulus molecule with a receptor/enzyme subsystem by, typically, binding to the macromolecule A and causing an activation or an inhibition of the subsystem by forming an

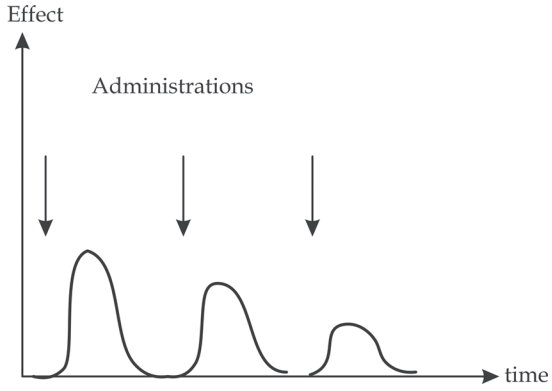


Fig 1-6: Tachyphylaxis

activated form of the macromolecule B. The following schematic represents the activity:

$$A \xrightarrow{p} B$$

where p is the activation rate coefficient. It is customary that p is called a rate constant, but, since p stands for measure of the intensity of the stimulus causing the activation, p may be variable (non-constant).

The above scheme is only the necessary condition for the rate sensitivity phenomenon, and other pathways of deactivation of B may be considered, with the subsequent return to the inactive form of the receptor/enzyme A.

Examples:

Calcitonin: Calcitonin demonstrates tachyphylaxis in 2–3 days when being used to treat hypercalcemia of malignancy. This reaction is anticipated and calcitonin is given along with bisphosphonates, which have their maximum effect in 2–3 days.

Hormone replacement: Hormone replacement when used in menopausal women in the form of estrogen and progesterone implants is cited as having potential to lead to tachyphylaxis, but that citation is based on a single study done in 1990 and no follow-up research is available to support this interpretation.

Psychedelics: Psychedelics such as LSD-25 and psilocybin containing mushrooms demonstrate very rapid tachyphylaxis. In other words, one may be unable to 'trip' two days in a row. Some people are able to 'trip' by taking up to three times the dosage, yet some users may not be able to negate tachyphylaxis at all until a period of days has gone by.

Centrally-acting analgesics: In a patient fully withdrawn from centrally-acting analgesics, *viz.*, opioids, going back to an intermittent schedule or maintenance dosing protocol, a fraction of the old tolerance level will rapidly develop, usually starting two days after opioid therapy is resumed and, in general, levelling off after day 7. Whether this is caused directly by opioid receptors modified in the past or effecting a change in some metabolic set-point is unclear. Increasing the dose will usually restore efficacy; relatively rapid opioid rotation may also be of use if the increase in tolerance continues.

Beta-2 adrenergic receptor gene: Gene encoding the beta-2 adrenergic receptor (ADRB2) is situated on chromosome 5q31. Individuals who are homozygous for the Gly16 form of the beta-2 adrenergic receptor gene have attenuated responses and more rapid tachyphylaxis to adrenergic bronchodilator medications than do those with the wild type, homozygous Arg16 form of the gene.

Nicotine: Nicotine may also show tachyphylaxis over the course of a day, although the mechanism of this action is unclear.

Other examples: Nitroglycerine demonstrates tachyphylaxis, requiring drug-free intervals when administered transdermally.

Repeated doses of ephedrine may display tachyphylaxis, since it is an indirectly acting sympathomimetic amine, which will deplete noradrenaline from the nerve terminal. Thus, repeated doses result in less noradrenaline released than the initial dose.

Hydralazine displays tachyphylaxis if given as a monotherapy for antihypertensive treatment. It is administered with a beta-blocker with or without a diuretic.

Metoclopramide is another example.

Dobutamine, a direct-acting beta agonist used in congestive heart failure, also demonstrates tachyphylaxis.

Desmopressin used in the treatment of type 1 von Willebrand disease is, in general, given every 12–24 hours in limited numbers due to its tachyphylactic properties.

Mechanisms that give rise to this phenomenon are :

1. Change in receptors (Rapid desensitization)
2. Loss of receptors (down-regulation)
3. Exhaustion of mediators
4. Increased metabolic degradation
5. Physiological adaptation

Change in receptors (Rapid desensitization): A slow conformational change in the receptor, resulting in tight binding of the agonist molecule without the opening of the ionic channel (e.g., ligand-gated ion channels such as nicotinic receptors at the neuromuscular junction) → rapid and reversible.

Phosphorylation of intracellular region of the receptor protein, leading to:

Desensitization of ion channel, or interference with the receptor's (e.g., GPCR) ability to activate second messenger cascade, though it can still bind the agonist molecule → slow and reversible.

Loss of receptors (down-regulation): Prolonged exposure to agonists often results in a gradual decrease in the actual number of receptors expressed on the cell surface. The vanishing receptors are taken into the cell by endocytosis of patches of the membrane; a process that also depends on phosphorylation. It occurs more slowly than rapid desensitization and is less readily reversible. This is because down-regulation involves a net degradation of receptors present in the cell, requiring new receptor biosynthesis for recovery, in contrast to rapid desensitization which involves reversible phosphorylation of existing receptors. Many G protein–coupled receptors and many hormone receptors are down-regulated by undergoing ligand-induced endocytosis and delivery to lysosomes. Down-regulation generally occurs only after prolonged or repeated exposure of cells to agonist (over hours to days).

Example: Chronic administration of salbutamol (β_2 agonist) can cause internalization of receptors → less receptors available for stimulation → decreased bronchodilation.

Exhaustion of mediators: Depletion of a signaling molecule or an essential intermediate substance required for biological response.

***Example* 1:** prolonged stimulation of G-protein coupled receptors can lead to depletion of intracellular secondary messengers.

***Example* 2:** Indirectly acting sympathomimetics (e.g. amphetamine) act by releasing tissue stores of adrenaline and noradrenaline and other amines from the nerve terminal → tachyphylaxis occurs because the amine stores become depleted.

Increased metabolic degradation: Increase in the rate of metabolism and/or elimination of drug. Lowers plasma drug concentrations.

Example: barbiturates and ethanol induce the expression of metabolic enzymes (cytochrome P450s) that degrade the drug → low plasma drug concentration.

Physiological adaptation: A drug's decreasing effects may occur because it is nullified by a homeostatic response. These homeostatic mechanisms are very common and if they occur slowly the result will be a very gradually developing tolerance.

***Example* 1:** The blood pressure-lowering effect of thiazide diuretics is limited because of a gradual activation of the renin-angiotensin system.

***Example* 2:** It is a common experience that many side effects of drugs such as nausea and sleepiness tend to subside even though administration is continued.

Tolerance: Resistance to normal therapeutic dose of drug, producing lesser response to normal therapeutic dose is known as tolerance. This is acquired character. Examples include morphine, person is initially responsive, if continued, changes occur at cellular and pharmacokinetic level, reducing the action. Thus one has to increase the dose of drug to overcome. Alcoholics do not respond to hypnotics and analgesics, dose of which has to be increased many folds. In fact they may even tolerate toxic levels.

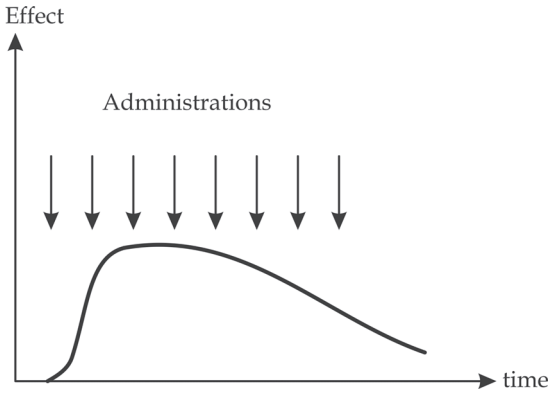


Fig 1-7: Tolerance

"Reduced responses to repeated administration of the same dose or increase in the dose are required to produce the same magnitude of response is called tolerance".

Types of Tolerance

True Tolerance: It is seen on both oral and parenteral administration of drug, and is divided into: Natural and Acquired.

Natural Tolerance: This is seen in various animal species and also among the human races. It includes.

- *Species tolerance:* Certain animal species can tolerate certain drugs in quantities that are lethal to man.

  Example: Rabbits can tolerate large quantities of belladona than humans due to presence of an enzyme atropine esterase that detoxifies it.
- *Racial tolerance:* Ephedrine solution when incorporated in to conjunctival sac in Caucasians it may produce pupil dilatation but not in Negros.

Acquired Tolerance: This type of tolerance unlike the racial and species tolerance develops only on repeated administration of drug. Many drugs like opiates, barbiturates, nitrites, and CNS depressants frequently develop tolerance. An uninterrupted presence of drug in the body favours the development of tolerance. However significant tolerance does not develop to atropine, digitalis, sodium nitroprusside and NSAIDs.

- ***Tissue tolerance:*** Tissue tolerance refers to the changes that occur on the tissue or cell that is affected by the drug.

  Example is barbiturates.
- ***Cross-tolerance:*** It refers to a pharmacological phenomenon, in which a patient being treated with a drug exhibits a physiological resistance to that medication as a result of tolerance to a pharmacologically similar drug. In other words, there is a decrease in response to one drug due to exposure to another similar acting drug. It is observed in treatment with antivirals, antibiotics and especially with opiate analgesics and many other medications including benzodiazepines.

  Cross-tolerance is particularly frequent amongst users of illicit drugs. For example, users with a high tolerance to the stimulant amphetamine may also exhibit a high tolerance to the structurally similar methamphetamine or other amphetamine-like stimulants. The phenomenon is also observed in cigarette smokers, in whom there is a demonstrably lessened sensitivity to the effects of caffeine. Cross-tolerance is also frequent in response to use of hallucinogens (e.g., LSD). General tolerance to the effects of tryptamines such as psilocybin, may be dramatic in response to repeated use, and this often translates into a tolerance to effects of other drugs such as mescaline. This is also true of benzodiazepines such as alprazolam and clonazepam, even opiates as well.

Pseudo Tolerance: It is confined to oral administration of drug. Example is feudal kings taking of small amounts of arsenic poison by mouth.

Mechanism of tolerance development

Pharmacokinetic tolerance: Pharmaco-kinetic tolerance - Also known as dispositional tolerance occurs because of a decreased quantity of the substance reaching the site it affects. This may be caused by an increase in induction of

the enzymes required for degradation of the drug e.g., CYP450 enzymes.

Pharmacodynamic tolerance: Also known as reduced responsiveness, the response to the substance is decreased by cellular mechanisms. This may be caused by a down regulation of receptor numbers.

Antagonism: When two drugs, administered simultaneously, oppose the action of each other on the same physiological system, the phenomenon is called antagonism. It can be of following types.

Chemical antagonism: It involves reduction of the biological activity of a drug by a chemical reaction with another agent e.g., between acids and alkalis: BAL (British anti lewisite) and arsenic. Antacids, used for dyspepsia involve administration of sodium bicarbonate to react with hydrochloric acid. In cases of heavy metal poisoning chelating agents are used like dimercaprol.

In iron poisoning deferoxamine is given which binds sulfhydryl groups forming insoluble complexes which can be easily detoxified.

Pharmacological antagonism: Pharmacological antagonism is of two types:

Competitive or reversible antagonism: In this type of antagonism the agonist and antagonist compete with each other for the same receptors. The extent of antagonism will depend on the relative number of receptors occupied by the two compounds. Other features are:

(a) Antagonist has chemical resemblance with agonist.
(b) Antagonism can be overcome by increasing the concentration of the agonist at receptor site. It means the maximal response to agonist is not impaired.
(c) Antagonist shifts the dose response curve to right.
(d) E_{max} of agonist is obtained with high concentration of agonist.
(e) Duration of action is short. It depends on drug clearance.

Example is of acetylcholine and atropine antagonism on muscarinic receptors. In presence of antagonist, log dose response curve of agonist shifts to right, indicating a higher concentration of agonist is required for same response. Maximum height of the curve can be attained by overcoming the action of antagonist. This leads to a parallel shift of log dose response curve towards right.

Non competitive antagonism: Here an antagonist inactivates the receptor(R) in such a way so that the effective complex with agonist cannot be formed irrespective of the concentration of the agonist. This can happen by various ways:

The antagonist might combine at the same site in such a way that even higher concentration of the agonist cannot displace it.

The antagonist might combine at a different site of R in such a way that agonist is unable to initiate characteristic biological response.

The antagonist might itself induce a certain change in R so that the reactivity of the receptor site where agonist should interact is abolished.

Other features of this antagonism are:

1. Antagonist has no chemical resemblance with agonist.
2. Maximum response is suppressed.
3. Although antagonist shifts the dose response curve to right, the slope of the curve is reduced.
4. The extent of antagonism depends on the characteristics of antagonist itself and agonist has no influence upon the degree of antagonism or its reversibility.
5. E_{max} of agonist is decreased even with high concentration of agonist.
6. Duration of action is long which depends upon new receptor synthesis.
7. Example is of phenoxybenzamine and adrenaline at alpha adrenergic receptors.

Physiological antagonism: In this interaction of two drugs, both are agonists, so they act at different receptor sites. They antagonize the action of each other because they produce opposite actions. Classical example of physiological antagonism is adrenaline and histamine. Former causes bronchodilatation while later bronchoconstriction. So adrenaline is a life saving drug in anaphylaxis. Acetylcholine slows the heart, and epinephrine accelerates it. Acetylcholine stimulates intestinal movement, and epinephrine inhibits it. Acetylcholine constricts the pupil, and epinephrine dilates it; and so on.

Pharmacokinetic antagonism: The situation in which the drug which may be termed the "antagonist" effectively reduces the concentration of the active drug (the "agonist") at its site of action. This may be due to an increase in metabolism or renal excretion of the "agonist" drug or to decreased absorption of the drug from the gastro-intestinal tract.

Example is warfarin and phenobarbital

Clinical significance of drug antagonism:

1. It helps to correct adverse effects of a drug e.g., ephedrine and phenobarbitone.
2. It is useful to treat drug poisoning e.g., morphine with naloxone.
3. It guides to avoid drug combinations with reduced drug efficacy such as penicillin and tetracycline combination.