I. Introduction to Pharmacology

Introduction to Pharmacology

The study of drugs or chemicals and the effects they have on living animals is called pharmacology. Pharmacology explains what drugs are, what they do to body functions and what the body does to them. Pharmacology also explains why a person may experience side effects when they take drugs and why there is such a wide spectrum of differences between drug actions in different people. Everyone at one stage or another in life will rely on a pharmaceutical product, whether it is for themselves, a friend or a family member. Therefore, it is useful to have a basic understanding of pharmacology.

Definitions – Pharmacology:

The study of drugs, their sources, their nature, and their properties. Pharmacology is the study of the body's reaction to drugs. It emerged as a major area in American medicine largely due to the efforts of John Jacob Abel (1857- 1938) who stressed the importance of chemistry in medicine, did research on the endocrine glands, first isolated epinephrine (adrenaline), crystallized insulin (1926), and became the first pharmacology professor in the U.S.

Pharmacokinetics:

Pharmacokinetics, derived from the Greek words pharmakon (drug) and kinetikos (movement), is used to describe the absorption, distribution, metabolism, and excretion of a compound. Although preclinical studies require the determination of acceptable in vitro activity and pharmacokinetics in at least two animal species, pharmacokinetic studies must be performed in man to correlate blood concentrations with particular biological effects. Knowledge of disposition in vivo is required to tailor modifications in order to eventually derive semisynthetic drugs. Pharmacokinetic studies of natural products are challenging because they typically involve the administration of complex mixtures of substances, in many instances of unknown components.

Pharmacokinetics (PK) describes how the concentration of a dosed drug and its metabolites in body fluids and tissues changes with time. PK models the concentration-time profile using key parameters, such as volume of distribution (Vd), area under the curve (AUC), clearance (CL), half-life (t1/2), maximum concentration (Cmax), and bioavailability (F). These parameters provide insights on how processes of the living system affect the drug concentration, including absorption, distribution, metabolism, and excretion. Owing to the dependence of PK parameters on the drug's properties, one application of PK in drug discovery is to derive insights about how the structure might be modified to improve the PK parameters. Since efficacy (i.e., pharmacodynamics) and toxicity are related to PK, pharmacokinetic/pharmacodynamic (PK/PD) models can be derived. These models are useful for planning and interpreting in vivo studies of efficacy and toxicity and planning human clinical trials.

Pharmacodynamics

Pharmacodynamics (sometimes described as what a drug does to the body) is the study of the biochemical, physiologic, and molecular effects of drugs on the body and involves receptor binding (including receptor sensitivity), post-receptor effects, and chemical interactions. Pharmacodynamics, with pharmacokinetics (what the body does to a drug, or the fate of a drug within the body), helps explain the relationship between the dose and response, ie, the drug's effects. The pharmacologic response depends on the drug binding to its target. The concentration of the drug at the receptor site influences the drug's effect.

A drug's pharmacodynamics can be affected by physiologic changes due to

- A disorder or disease
- Aging process

- Other drugs

Disorders that affect pharmacodynamic responses include genetic mutations, thyrotoxicosis, malnutrition, myasthenia gravis, Parkinson disease, and some forms of insulin-resistant diabetes mellitus. These disorders can change receptor binding, alter the level of binding proteins, or decrease receptor sensitivity.

Aging tends to affect pharmacodynamic responses through alterations in receptor binding or in post-receptor response sensitivity (see table Effect of Aging on Drug Response). Pharmacodynamic drug–drug interactions result in competition for receptor binding sites or alter post-receptor response.

Drug:

A drug is any substance that causes a change in an organism's physiology or psychology when consumed. Drugs are typically distinguished from food and substances that provide nutritional support. Consumption of drugs can be via inhalation, injection, smoking, ingestion, absorption via a patch on the skin, or dissolution under the tongue.

In pharmacology, a drug is a chemical substance, typically of known structure, which, when administered to a living organism, produces a biological effect. A pharmaceutical drug, also called a medication or medicine, is a chemical substance used to treat, cure, prevent, or diagnose a disease or to promote well-being. Traditionally drugs were obtained through extraction from medicinal plants, but more recently also by organic synthesis. Pharmaceutical drugs may be used for a limited duration, or on a regular basis for chronic disorders.

Pharmaceutical drugs are often classified into drug classes—groups of related drugs that have similar chemical structures, the same mechanism of action (binding to the same biological target), a related mode of action, and that are used to treat the same disease. The Anatomical Therapeutic Chemical Classification System (ATC), the most widely used drug classification system, assigns drugs a unique ATC code, which is an alphanumeric code that assigns it to specific drug classes within the ATC system. Another major classification system is the Biopharmaceutics Classification System. This classifies drugs according to their solubility and permeability or absorption properties.

Psychoactive drugs are chemical substances that affect the function of the central nervous system, altering perception, mood or consciousness. These drugs are divided into different groups like: stimulants, depressants, antidepressants, anxiolytics, antipsychotics, and hallucinogens. These psychoactive drugs have been proven useful in treating wide range of medical conditions including mental disorders around the world. The most widely used drugs in the world include caffeine, nicotine and alcohol, which are also considered recreational drugs, since they are used for pleasure rather than medicinal purposes. Abuse of several psychoactive drugs can cause psychological or physical addiction. It's worth noting that all drugs can have potential side effects. Excessive use of stimulants can promote stimulant psychosis. Many recreational drugs are illicit and international treaties such as the Single Convention on Narcotic Drugs exist for the purpose of their prohibition

Pharmacotherapeutics:

Pharmacotherapeutics is the clinical purpose or indication for giving a drug. Pharmacokinetics is the effect of the body on the drug. It is made up of four phases: absorption, distribution, metabolism, and excretion. Absorption is the movement of the drug from the site of administration into the bloodstream. Distribution is movement of the drug through the bloodstream and eventually into the cells. Metabolism refers to the changing of the drug into another substance or substances (i.e., metabolites). Excretion is the removal of the drug or its metabolites from the body. Metabolism and excretion are considered together as elimination of a drug. Most commonly in practice, however, the clinician uses the term

elimination as a synonym excretion. The blood-brain barrier is the body's natural defense to keep toxins and poisons from reaching the brain. It also may prevent the distribution of needed drug molecules from reaching their target. Drugs have different affi nities for protein molecules, especially albumin, in the blood. Drugs that are highly protein bound have a lower proportion of their molecules available to produce the desired therapeutic effect. Only the free drug is active. Metabolism of drugs occurs primarily in the liver. Liver metabolism is predominantly achieved by specific liver enzymes, known as the P-450 system. The P-450 system also metabolizes some drug in the small intestine. Some drugs can induce this system, increasing their own or other drugs' metabolism. When multiple drugs are metabolized by the same P-450 family, the metabolism of all the drugs is normally decreased. Anything that impairs liver functioning also decreases drug metabolism. Decreased metabolism leads to increased circulating levels of the drug, more therapeutic effect, and possibly more adverse effects. Drugs that are administered orally pass through the liver before going to the general circulation. If the drug is highly metabolized, a high fi rst-pass effect occurs. This effect substantially decreases the amount of drug that is distributed to the body. The kidney is the primary organ responsible for drug excretion. There are three processes that affect the excretion of drugs in the urine: glomerular filtration, passive tubular reabsorption, and active tubular secretion. Anything that decreases kidney function decreases drug excretion, leading to increased circulating blood levels of the drug. Half-life of a drug is the amount of time needed to eliminate (by metabolism and excretion) half of the drug molecules currently in the body. Steady state is when the continuing dose of a drug is in balance with the elimination rate of the drug, that is, when the amount of drug entering the body equals the amount being removed. Steady state is achieved after four to five half-lives. Achievement of steady state is not related to the dosage of the drug or the frequency of drug administration. Most drugs create their effects in the body by attaching to special sites, called receptors, on cells. At the receptor site, the drug is able to stimulate the cell to act in a way that the cell is designed to act. Drugs that stimulate the cell to act are known as agonists. Drugs that attach to receptors to prevent other substances from attaching and "turning on" the cell are called antagonists or blockers. The single occupancy theory and the modified occupancy theory help to explain how drugs achieve their effects at receptors. Potency of a drug refers to how much of a drug is needed to create the desired therapeutic effect. Efficacy of a drug refers to how well the drug creates the desired therapeutic effect. Drugs may have different potencies but the same efficacy. Efficacy is a more important consideration than potency when selecting a particular drug. Loading doses are larger-than-normal doses used when therapy is initiated with drugs that have very long half-lives. The purpose of the loading dose is to achieve quickly a blood level of the drug that is in therapeutic range even though the drug has not reached steady state. Maintenance doses are the doses administered regularly throughout therapy. The therapeutic index is a measurement of the safety of the drug. Drugs that are described as having a narrow therapeutic index do not have much difference between the effective dose and the toxic or lethal dose. Patients receiving these drugs need to be monitored very closely for adverse effects. They also need to have their drug blood levels monitored closely. Drug dosages are adjusted to maintain a therapeutic level of the drug. Drug blood levels are one way of determining whether a dose needs to be either increased or decreased.

Clinical pharmacology:

It is underpinned by the basic science of pharmacology, with added focus on the application of pharmacological principles and methods in the real world. It has a broad scope, from the discovery of new target molecules, to the effects of drug usage in whole populations.

Clinical pharmacologists are physicians, pharmacists, and scientists whose focus is developing and understanding new drug therapies. Clinical pharmacologists work in a variety of settings in academia, industry and government. In the laboratory setting they study biomarkers, pharmacokinetics, drug metabolism and genetics. In the office setting they design and evaluate clinical trials, create and implement regulation guidelines for drug use, and look at drug utilization on local and global scales. In the clinical setting they work directly with patients, participate in experimental studies, and investigate adverse reactions and interactions.

Clinical Pharmacology, in theory, has been practiced for centuries through observing the effects of herbal remedies and early drugs on humans. Most of this work was done through trial and error. In the early 1900s, scientific advances allowed scientists to combine the study of physiological effects with biological effects. This led to the first major breakthrough when scientists used clinical pharmacology to discover insulin. Since that discovery clinical pharmacology has expanded to be a multidisciplinary field and has contributed to the understanding of drug interaction, therapeutic efficacy and safety in humans. Over time clinical pharmacologists have been able to make more exact measurements and personalize drug therapies.

Chemotherapy:

Chemotherapy is a drug treatment that uses powerful chemicals to kill fast-growing cells in your body. Chemotherapy is most often used to treat cancer, since cancer cells grow and multiply much more quickly than most cells in the body. Many different chemotherapy drugs are available. Chemotherapy drugs can be used alone or in combination to treat a wide variety of cancers. Though chemotherapy is an effective way to treat many types of cancer, chemotherapy treatment also carries a risk of side effects. Some chemotherapy side effects are mild and treatable, while others can cause serious complications.

Chemotherapy is used to kill cancer cells in people with cancer. There are a variety of settings in which chemotherapy may be used in people with cancer:

- To cure the cancer without other treatments. Chemotherapy can be used as the primary or sole treatment for cancer.
- After other treatments, to kill hidden cancer cells. Chemotherapy can be used after other treatments, such as surgery, to kill any cancer cells that might remain in the body. Doctors call this adjuvant therapy.
- To prepare you for other treatments. Chemotherapy can be used to shrink a tumour so that other treatments, such as radiation and surgery, are possible. Doctors call this neoadjuvant therapy.
- To ease signs and symptoms. Chemotherapy may help relieve signs and symptoms of cancer by killing some of the cancer cells. Doctors call this palliative chemotherapy.

Some chemotherapy drugs have proved useful in treating other conditions, such as:

- Bone marrow diseases. Diseases that affect the bone marrow and blood cells may be treated with a bone marrow transplant, also known as a stem cell transplant. Chemotherapy is often used to prepare for a bone marrow transplant.
- Immune system disorders. Lower doses of chemotherapy drugs can help control an overactive immune system in certain diseases, such as lupus and rheumatoid arthritis.

Pharmacy and Toxicology

Pharmacology and toxicology are very similar disciplines that require an understanding of basic properties and actions of chemicals. However, pharmacology places more emphasis on the therapeutic effects of chemicals (particularly drugs) while toxicology focusses more on the adverse effects of chemicals and risk assessment.

Pharmacology is the study of drugs. It involves examining the interactions of chemical substances with living systems, with a view to understanding the properties of drugs and their actions, including the interactions between drug molecules and drug receptors and how these interactions elicit an effect. Our pharmacology courses examine the different classes of drugs, how they are used therapeutically, their mechanisms of action, how they are handled by the human body, and their role in society.

Pharmacology provides the scientific basis and principles for a variety of special applications, such as the study of drug actions in the health sciences, the use of drugs as therapeutic agents in medicine or as tools in scientific research, and the development and regulation of pharmaceuticals. Pharmacology is a multi-disciplinary science with many subspecialties including clinical pharmacology, cardiovascular pharmacology, behavioural pharmacology, neuropsychopharmacology, pharmacogenetics, and pharmaco-economics, to name a few.

Toxicology is the study of the adverse effects of chemicals (including drugs) on living systems and the means to prevent or ameliorate such effects. In addition to therapeutic agents, toxicologists examine many environmental agents and chemical compounds that are synthesized by humans or that originate in nature. The toxic effects of these agents may range from disturbances in growth patterns, discomfort, disease or death of individual organisms or on whole ecosystems. There are many subspecialties of toxicology including: clinical toxicology, regulatory toxicology (both of these found in the pharmaceutical and toxicology industry), forensic toxicology, occupational toxicology, and risk assessment. The current need for toxicologists is outlined in a recent online Science publication.

Pharmacology programs are distinct programs from the Pharmacy program. Pharmacology programs are joint undergraduate programs between the Faculty of Arts and Science and the Faculty of Medicine. Students graduating with an undergraduate Specialist or Major program in Pharmacology receive a Bachelor of Science degree. Pharmacy is a professional degree program offered by the Faculty of Pharmacy that prepares students to become licensed pharmacists. A license is required to legally dispense drugs.

Drug Nomenclature – *Refer the appendix*

Routes of drug administration

Drugs are introduced into the body by several routes. They may be

- → Taken by mouth (orally).
- → Given by injection into a vein (intravenously, IV), into a muscle (intramuscularly, IM), into the space around the spinal cord (intrathecally), or beneath the skin (subcutaneously, sc).
- → Placed under the tongue (sublingually) or between the gums and cheek (buccally)
- → Inserted in the rectum (rectally) or vagina (vaginally).
- → Placed in the eye (by the ocular route) or the ear (by the otic route).
- → Sprayed into the nose and absorbed through the nasal membranes (nasally).
- → Breathed into the lungs, usually through the mouth (by inhalation) or mouth and nose (by nebulization).
- → Applied to the skin (cutaneous) for a local (topical) or body wide (systemic) effect.
- → Delivered through the skin by a patch (trans dermally) for a systemic effect Each route has specific purposes, advantages, and disadvantages.

Oral route

Many drugs can be administered orally as liquids, capsules, tablets, or chewable tablets. Because the oral route is the most convenient and usually the safest and least expensive, it is the one most often used. However, it has limitations because of the way a drug typically moves through the digestive tract. For drugs administered orally, absorption

may begin in the mouth and stomach. However, most drugs are usually absorbed from the small intestine. The drug passes through the intestinal wall and travels to the liver before being transported via the bloodstream to its target site. The intestinal wall and liver chemically alter (metabolize) many drugs, decreasing the amount of drug reaching the bloodstream. Consequently, these drugs are often given in smaller doses when injected intravenously to produce the same effect.

When a drug is taken orally, food and other drugs in the digestive tract may affect how much of and how fast the drug is absorbed. Thus, some drugs should be taken on an empty stomach, others should be taken with food, others should not be taken with certain other drugs, and still others cannot be taken orally at all.

Some orally administered drugs irritate the digestive tract. For example, aspirin and most other nonsteroidal anti-inflammatory drugs (NSAIDs) can harm the lining of the stomach and small intestine to potentially cause or aggravate preexisting ulcers. Other drugs are absorbed poorly or erratically in the digestive tract or are destroyed by the acid and digestive enzymes in the stomach.

Other routes of administration are required when the oral route cannot be used, for example:

→ When a person cannot take anything by mouth
→ When a drug must be administered rapidly or in a precise or very high dose
→ When a drug is poorly or erratically absorbed from the digestive tract

Injection routes

Administration by injection (parenteral administration) includes the following routes:

→ Subcutaneous (under the skin)
→ Intramuscular (in a muscle)
→ Intravenous (in a vein)
→ Intrathecal (around the spinal cord)

A drug product can be prepared or manufactured in ways that prolong drug absorption from the injection site for hours, days, or longer. Such products do not need to be administered as often as drug products with more rapid absorption.

Through the Skin

Sometimes a drug is given through the skin—by needle (subcutaneous, intramuscular, or intravenous route) route), or by implantation. For the subcutaneous route, a needle is inserted into fatty tissue just beneath the skin. After a drug is injected, it then moves into small blood vessels (capillaries) and is carried away by the bloodstream. Alternatively, a drug reaches the bloodstream through the lymphatic vessels (see Figure: Lymphatic System: Helping Defend Against Infection). Protein drugs that are large in size, such as insulin, usually reach the bloodstream through the lymphatic vessels because these drugs move slowly from the tissues into capillaries. The subcutaneous route is used for many protein drugs because such drugs would be destroyed in the digestive tract if they were taken orally.

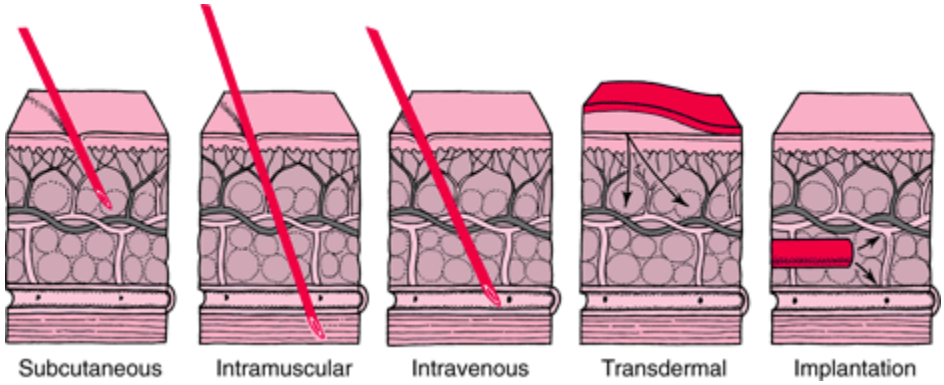

Figure1.1 Types of injections

Certain drugs (such as progestins used for hormonal birth control) may be given by inserting plastic capsules under the skin (implantation). Although this route of administration is rarely used, its main advantage is to provide a long-term therapeutic effect (for example, etonogestrel that is implanted for contraception may last up to 3 years).

The intramuscular route is preferred to the subcutaneous route when larger volumes of a drug product are needed. Because the muscles lie below the skin and fatty tissues, a longer needle is used. Drugs are usually injected into the muscle of the upper arm, thigh, or buttock. How quickly the drug is absorbed into the bloodstream depends, in part, on the blood supply to the muscle: The sparser the blood supply, the longer it takes for the drug to be absorbed.

For the intravenous route, a needle is inserted directly into a vein. A solution containing the drug may be given in a single dose or by continuous infusion. For infusion, the solution is moved by gravity (from a collapsible plastic bag) or, more commonly, by an infusion pump through thin flexible tubing to a tube (catheter) inserted in a vein, usually in the forearm.

Intravenous administration is the best way to deliver a precise dose quickly and in a well- controlled manner throughout the body. It is also used for irritating solutions, which would cause pain and damage tissues if given by subcutaneous or intramuscular injection. An intravenous injection can be more difficult to administer than a subcutaneous or intramuscular injection because inserting a needle or catheter into a vein may be difficult, especially if the person is obese.

When given intravenously, a drug is delivered immediately to the bloodstream and tends to take effect more quickly than when given by any other route. Consequently, health care practitioners closely monitor people who receive an intravenous injection for signs that the drug is working or is causing undesired side effects. Also, the effect of a drug given by this route tends to last for a shorter time. Therefore, some drugs must be given by continuous infusion to keep their effect constant.

For the intrathecal route, a needle is inserted between two vertebrae in the lower spine and into the space around the spinal cord. The drug is then injected into the spinal canal. A small amount of local anesthetic is often used to numb the injection site. This route is used when a drug is needed to produce rapid or local effects on the brain, spinal cord, or the layers of tissue covering them (meninges)—for example, to treat infections of these structures. Anesthetics and analgesics (such as morphine) are sometimes given this way.

Sublingual and buccal routes

A few drugs are placed under the tongue (taken sublingually) or between the gums and teeth (buccally) so that they can dissolve and be absorbed directly into the small blood vessels that lie beneath the tongue. These drugs are not swallowed. The sublingual route is especially good for nitroglycerin, which is used to relieve angina, because absorption is rapid

and the drug immediately enters the bloodstream without first passing through the intestinal wall and liver. However, most drugs cannot be taken this way because they may be absorbed incompletely or erratically.

Rectal route

Many drugs that are administered orally can also be administered rectally as a suppository. In this form, a drug is mixed with a waxy substance that dissolves or liquefies after it is inserted into the rectum. Because the rectum's wall is thin and its blood supply rich, the drug is readily absorbed. A suppository is prescribed for people who cannot take a drug orally because they have nausea, cannot swallow, or have restrictions on eating, as is required before and after many surgical operations. Drugs that can be administered rectally include acetaminophen (for fever), diazepam (for seizures), and laxatives (for constipation). Drugs that are irritating in suppository form may have to be given by injection.

Vaginal route

Some drugs may be administered vaginally to women as a solution, tablet, cream, gel, suppository, or ring. The drug is slowly absorbed through the vaginal wall. This route is often used to give estrogen to women during menopause to relieve vaginal symptoms such as dryness, soreness, and redness.

Ocular route

Drugs used to treat eye disorders (such as glaucoma, conjunctivitis, and injuries) can be mixed with inactive substances to make a liquid, gel, or ointment so that they can be applied to the eye. Liquid eye drops are relatively easy to use but may run off the eye too quickly to be absorbed well. Gel and ointment formulations keep the drug in contact with the eye surface longer, but they may blur vision. Solid inserts, which release the drug continuously and slowly, are also available, but they may be hard to put in and keep in place.

Ocular drugs are almost always used for their local effects. For example, artificial tears are used to relieve dry eyes. Other drugs (for example, those used to treat glaucoma [see table Drugs Used to Treat Glaucoma], such as acetazolamide and betaxolol, and those used to dilate pupils, such as phenylephrine and tropicamide) produce a local effect (acting directly on the eyes) after they are absorbed through the cornea and conjunctiva. Some of these drugs then enter the bloodstream and may cause unwanted side effects on other parts of the body.

Otic route

Drugs used to treat ear inflammation and infection can be applied directly to the affected ears. Ear drops containing solutions or suspensions are typically applied only to the outer ear canal. Before applying ear drops, people should thoroughly clean the ear with a moist cloth and dry it. Unless the drugs are used for a long time or used too much, little of the drugs enter the bloodstream, so body wide side effects are absent or minimal. Drugs that can be given by the otic route include hydrocortisone (to relieve inflammation), ciprofloxacin (to treat infection), and benzocaine (to numb the ear).

Nasal route

If a drug is to be breathed in and absorbed through the thin mucous membrane that lines the nasal passages, it must be transformed into tiny droplets in air (atomized). Once absorbed, the drug enters the bloodstream. Drugs administered by this route generally work quickly. Some of them irritate the nasal passages. Drugs that can be administered by the nasal route include nicotine (for smoking cessation), calcitonin (for osteoporosis), sumatriptan (for migraine headaches), and corticosteroids (for allergies).

Inhalation route

Drugs administered by inhalation through the mouth must be atomized into smaller droplets than those administered by the nasal route, so that the drugs can pass through the

windpipe (trachea) and into the lungs. How deeply into the lungs they go depends on the size of the droplets. Smaller droplets go deeper, which increases the amount of drug absorbed. Inside the lungs, they are absorbed into the bloodstream.

Inhalers

Relatively few drugs are administered this way because inhalation must be carefully monitored to ensure that a person receives the right amount of drug within a specified time. In addition, specialized equipment may be needed to give the drug by this route. Usually, this method is used to administer drugs that act specifically on the lungs, such as aerosolized antiasthmatic drugs in metered-dose containers (called inhalers), and to administer gases used for general anesthesia.

Nebulization route

Similar to the inhalation route, drugs given by nebulization must be aerosolized into small particles to reach the lungs. Nebulization requires the use of special devices, most commonly ultrasonic or jet nebulizer systems. Using the devices properly helps maximize the amount of drug delivered to the lungs. Drugs that are nebulized include tobramycin (for cystic fibrosis), pentamidine (for pneumonia caused by Pneumocystis jirovecii), and albuterol (for asthma attacks).

Side effects can include those that occur when the drug is deposited directly in the lungs (such as cough, wheezing, shortness of breath, and lung irritation), spread of the drug into the environment (possibly affecting people other than the one taking the drug), and contamination of the device used for nebulization (particularly when the device is reused and inadequately cleaned). Using the device properly helps prevent side effects.

Cutaneous route

Drugs applied to the skin are usually used for their local effects and thus are most commonly used to treat superficial skin disorders, such as psoriasis, eczema, skin infections (viral, bacterial, and fungal), itching, and dry skin. The drug is mixed with inactive substances. Depending on the consistency of the inactive substances, the formulation may be an ointment, cream, lotion, solution, powder, or gel (see Topical Preparations).

Transdermal route

Some drugs are delivered body wide through a patch on the skin. These drugs are sometimes mixed with a chemical (such as alcohol) that enhances penetration through the skin into the bloodstream without any injection. Through a patch, the drug can be delivered slowly and continuously for many hours or days or even longer. As a result, levels of a drug in the blood can be kept relatively constant. Patches are particularly useful for drugs that are quickly eliminated from the body because such drugs, if taken in other forms, would have to be taken frequently. However, patches may irritate the skin of some people. In addition, patches are limited by how quickly the drug can penetrate the skin. Only drugs to be given in relatively small daily doses can be given through patches. Examples of such drugs include nitroglycerin (for chest pain), scopolamine (for motion sickness), nicotine (for smoking cessation), clonidine (for high blood pressure), and fentanyl (for pain relief).

Dosage forms of Drug

Licensed drugs are available in a wide variety of formulations including liquids for oral administration, injectable solutions, ointments or gels, transdermal patches, tablets, capsules, suppositories, and inhaled aerosols. The selection of a particular dosage form and route of administration will depend upon both the clinical circumstances, and the characteristics of the drug. While oral administration is the most common route used, some drugs are poorly absorbed when taken orally. In some clinical situations (e.g. the patient is unconscious) the oral route may not be viable, or a route producing a more rapid onset of

action may be necessary. This module summarizes the major drug formulations, their major characteristics and their most common clinical uses.

Solid Dosage Forms

Tablet – a solid dosage form made using a mold Compressed tablet

Tablets are one of the most frequently used dosage forms, and they are typically made by a commercial process involving compression of a drug-containing mixture of materials in a high-throughput tableting machine.

The quantity of drug (or drug dose) in each tablet is determined by the manufacturer. In most tableting machines, a tablet is formed by the pressing action of two punches and a die that involves a series of automated steps that include:

- → downward movement of a lower punch located within a hole in a die to allow drug-containing powder to fill the die cavity from a medication "feeder".
- → scrapping off the excess tablet material from the top of the die.
- → compressing the material into a hard tablet by lowering an upper punch into the hole of the die.
- → raising the lower punch to eject the tablet.

In the formulation of the mixture for tableting, the manufacturer uses multiple (e.g. up to 20) substances in addition to the active drug. These commonly include ingredients to cause a rapid break-up of the tablet when moistened, substances to promote the stability of the active ingredient, and/or substances that bind the active ingredient to modify its rate of going into solution and being absorbed. This is part of the process that can result in different formulations of medications that contain the same amount of active ingredient having very different kinetics with regard to the release and subsequent absorption of the active ingredient, or different bioavailability. However, in general, generic drug formulations almost always have the same bioavailability as the proprietary patent formulations they are designed to replace (and at a lower cost) (Gavura, 2012).

Hand held tablet presses

More simple hand-held mini tablet press kits, such as illustrated on this YouTube video have the capability to create non-commercial tablets containing anything from mixtures of vitamins to illegal street drugs, such as MDMA (Figure 1.2).

Figure 1.2. Illegal non-commercial tablets containing the street drug MDMA (ecstasy) obtained by a DEA employee. Reproduced from the Wikipedia commons.

Tablet coatings

Tablet coatings can serve multiple functions:

→ They can mask an undesirable taste and facilitate swallowing.

→ They can provide a means of easy visual identification, to discriminate one medication from another (many elderly patients take several medications a day, and place them in 7-day pill containers to increase compliance to their daily drug regimen).

→ "Enteric coatings (EC)" are sometimes used to delay dissolution until the tablet passes through the stomach and reaches the duodenum. Enteric coatings are stable in highly acidic environments (pH 1-3), but break down under less acidic conditions (pH 7-9). They can be made of numerous substances including plant fibers, fatty acids or plastics.

→ Enteric coatings are employed with substances that are either unstable in the low pH of the stomach (e.g. erythromycin), substances that are irritating to the gastric mucosa (e.g. aspirin), or to prevent unpleasant symptoms related to oral reflux (e.g. "fish burps" associated with fish oil supplements)1).

Identifying Tablets

Tablet identifiers & markings

By Federal regulation, all solid oral dosage forms (tablet or capsule) must be imprinted with a unique code. This code as well as the product's regulated size, shape and color permits the identification of the drug product, dosage and the manufacturer of the product. For example, as illustrated in Figure 3, only generic 20 mg dose tablets of prednisone made by Qualitest Pharmaceuticals have the following unique identifying characteristics:

- shape: round
- size: 10 mm
- color: peach/orange
- imprint code: 5092
- manufactuter code: V (for Qualitest Pharmaceuticals)

Similar information for any solid medication can be used to identify it using online databases including:

- Rxlist.com Pill Identification Tool
- Epocrates commercial software
- Pillbox rapid identification database provided by the National Library of Medicine & NIH

When treating a patient suffering from an apparent drug overdose, identification of legally made tablets (e.g. containing a narcotic, amphetamine or a benzodiazepine) can be useful in making a diagnosis (as in the clinical case of cousin Dalton).

Note that the example shown for the illegal street drug MDMA (Figure 1.2) lacks these standardized licensed colors and imprints. As a result, accurate identification of the active ingredients in unlicensed or "home-made" tablets will likely require time-consuming chemical analysis, toxicology blood tests and/or a definitive clinical diagnosis.

Tablet Scoring

Tablets often contain an indented line that runs across the surface of the tablet that assists in the practice of cutting or breaking the tablet into smaller portions so that a lower dosage can be administered. Scored tablets must contain an equally distributed percentage of active ingredient in each portion when they are divided.

Figure 1.3. Prednisone 20 mg tablets. Each tablet has a specific color (orange/peach), shape (round), size (10 mm diameter), absence or presence of a score (in this example one that can be used to split the tablet into 2 halves), and drug label imprint (5092 on one side, V on the opposite side). Reproduced from Wikipedia Commons.

Time Release or Extended Release Technologies

There are several different designations for patented mechanisms used in tablets or capsules to allow a drug to dissolve over time in order to provide a steady release into the bloodstream, and reduce the need for frequent dosing. Names associated with these technologies include.

- SR - sustained release
- SA - sustained action
- ER, XR, XL - extended release
- TR - timed release
- CR - controlled release
- MR - modified release

One example of an extended release system is a tablet that employs osmotic pressure to deliver drug at a zero order rate, i.e. independent of pH or intestinal motility. The core of drug is surrounded by a semi-permeable membrane that has been pierced by a laser-hole. The movement of water into the core pushes dissolved drug out through the hole. This provides a very stable rate of delivery of drug, typically for 12-24 hours. The decreased number of doses required increases the likelihood of correct compliance with the schedule of taking the formulation.

Other means of delaying absorption include incorporation of the drug into a waxy matrix or within a polymer that slowly dissolves and releases the drug for subsequent absorption.

Tablet triturate (e.g. Nitroglycerin tablets)

→ The tablet mass is made up of the active drug along with glucose, lactose or sucrose that is moistened with alcohol. The slurry is pressed into the holes in a mold, then an appropriately-sized small pillar is pushed through the hole and the resultant tablet is allowed to air dry.

→ This process creates a very friable tablet that rapidly dissolves in the presence of moisture (e.g. when placed under the tongue). Sublingual placement of nitroglycerin triturate tablets is indicated for the rapid relief from ischemic chest pain (exertional

angina), The therapeutic onset of action typically occurs within 1-3 minutes after sublingual placement (rxlist.com-absorption).

→ Alternatively, if a drug is to be administered as an injection, the triturate is made under sterile conditions. These are usually called "hypodermic tablets" (e.g. tablet triturates containing morphine sulfate).

Orally Disintegrating Tablets & Films (ODTs & ODFs)

New forms of rapid drug delivery using orally disintegrating tablets (ODTs) or thin dissolving films are becoming more popular.

These solid tablets rapidly disintegrate in a matter of seconds when placed on the tongue, and have been designed for a variety of indications (Wikipedia). ODTs dissolve more rapidly than conventional sublingual or buccal tablets or lozenges that require more than a minute to dissolve in the oral cavity. Depending on the chemistry of the drug, the active ingredient can be absorbed either through mucous membranes in the mouth, or across the GI tract once the drug-containing saliva is swallowed (Hirani et al, 2009). This dosage form is most suitable for patients or conditions that include:

→ pediatric patients under 10 years of age who have difficulty swallowing tablets or capsules. geriatric patients with dysphagia (up to 60% of elderly institutionalized patients suffer from dysphagia).

→ patients with conditions where a fast-onset is therapeutically important e.g. rizatriptan ODT - Maxalt ® to abort a migraine headache.

→ patients that are too nauseous to swallow a tablet or capsule e.g. ondansetron ODT - Zofran ® for prevention of nausea & vomiting.

→ patients with little or no access to water institutionalized schizophrenic patients who may try to hide conventional tablets under their tongue to avoid their daily dose of an antipsychotic drug e.g. olanzepine ODT - Zyprexa Zydis ®

ODFs

Orally dissolving films (ODFs) are fast dissolving strips that are similar to the size, thickness and shape as a postage stamp. They can be placed either on top of the tongue, under the tongue (sublingual), or alongside the cheek (buccal). In most cases this delivery option allows the drug to be absorbed across the oral mucosa, bypassing the GI tract and first-pass metabolism, which increases both the speed of onset of the drug, and its bioavailability (Bala et al, 2013). Examples include:

→ Suboxone ®: buprenorphine and naloxone for opioid addiction

→ Zuplenz ®: ondansetron soluble film

Capsule

Drug capsules come in two common varieties, "single piece soft capsules" and "two piece hard capsules".

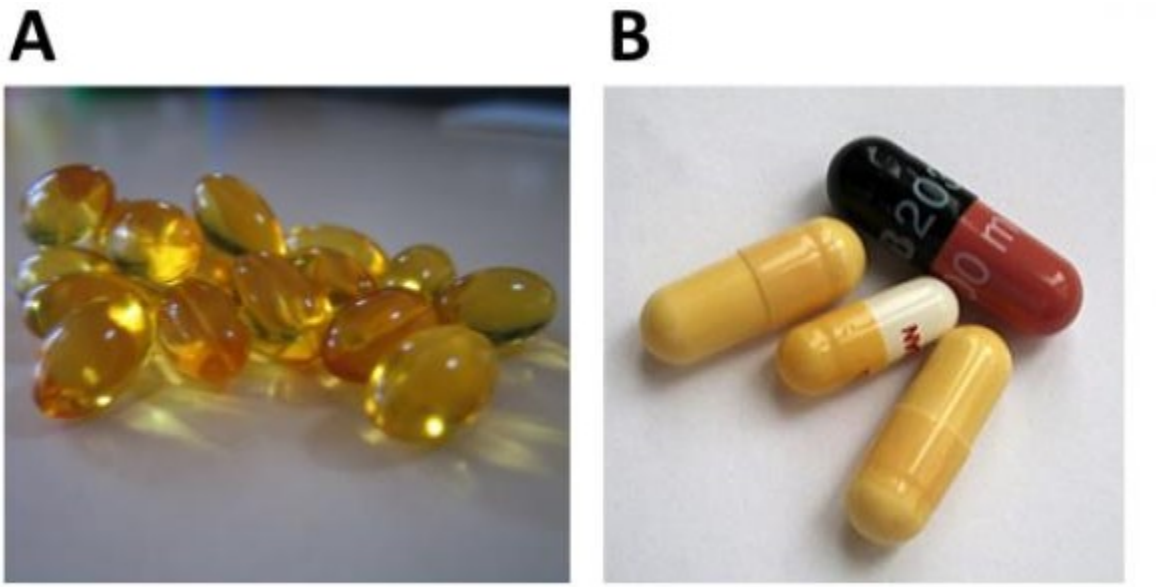

Figure 1.4. The two most common types of capsules. A) Single piece "soft gels" (from Wikipedia Commons). B) Two piece "hard capsules" (from Wikipedia Commons).

Soft Capsules

These typically consist of a single piece shell consisting of gelatin, water, an opacifier and a plasticiser such as glycerin (Wikipedia). In many cases they provide an effective means of oral delivery for poorly soluble drugs because they can be filled with liquid ingredients that increase solubility that would be difficult to include in a solid tablet. Examples include:

- Neoral ®: cyclosporine soft gelatin capsules
- Invirase ®: saquinavir HIV-1 protease inhibitor
- Omtryg ®: omega-3 soft capsules
- Sonata ®: zaleplon sleep aid capsules

Hard Capsules

Commonly made of hard gelatin (Figure 1.4B). The two parts fit together to enclose the medication, preservatives and other ingredients that are in powder or pellet form. The capsule cover masks the taste of the ingredients (i.e., salty or bitter), and makes it more palatable. Also, the gelatin, when moist, slips down the throat easier and makes it easier to swallow. The two parts can be colored to aid in identification and coatings can be put on it to alter the site of dissolution. Like tablets, capsules may also contain diluents, lubricants or dispersants. Examples include:

- Lyrica ®: for fibromyalgia & neuropathic pain
- Flomax ®: alpha blocker for treatment of male benign prostatic hyperplasia (BPH)
- Verelan ®: calcium channel blocker for hypertension

Murders related to hard capsule tampering in the 1980s. Historically, over-the-counter hard capsules have had their issues with incidents where they have been tampered with, resulting in intentional poisoning deaths when Tylenol capsules were removed from store shelves, laced with potassium cyanide, and replaced on store shelves in the Chicago area in 1982, followed by a copycat incident in Washington state in 1986. This resulted in reforms in the packaging of over-the-counter products to make them more tamper resistant.

Suppositories

Figure 1.5. Glycerin laxative suppository. Reproduced from the Wikipedia Commons.

These come in solid or semi-solid dosage forms intended for insertion into a body cavity or orifice other than the mouth (e.g. rectal or vaginal). The vehicle either melts or dissolves following insertion. They are used for local effect (e.g. as a laxative, or treatment for colitis) or for systemic absorption when the individual cannot easily take medication orally (e.g., vomiting or unconscious). Examples include:

- Glycerin laxative suppository
- Canasa ®: mesalamine rectal suppository for ulcerative colitis.
- Promethazine suppository: for nausea & vomiting, motion sickness, allergy.

Ointments & Gels

These are solid or semi-solid preparations intended for application to the body surface or mucous membranes.

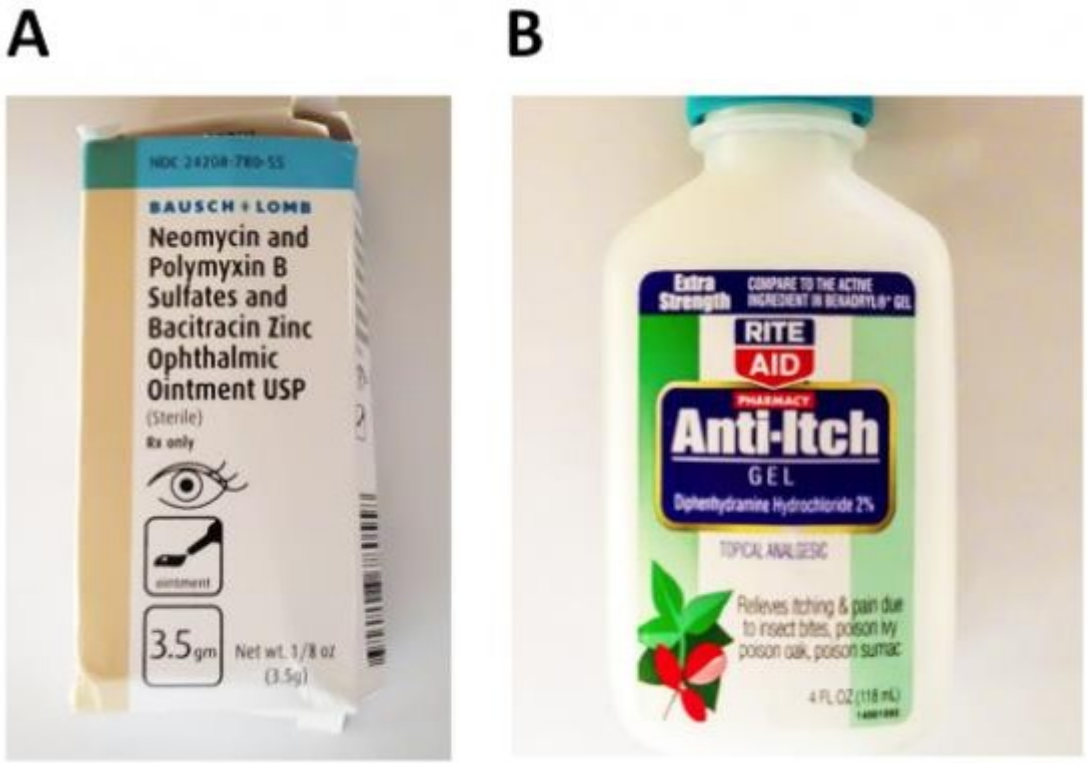

Figure 1.6. Ointments & Gels. A) Antibiotic ointment for eye infections. B) Anti-itch diphenhydramine gel.

Examples include:

- AndroGel ®: testosterone gel for androgen replacement therapy
- Zovirax ®: acyclovir for genital herpes
- Amcinonide ®: topical corticosteroid for relief from inflammation

Transdermal Patch

This is a rapidly developing dosage formulation for topical application of medication for systemic absorption. They look very much like a Band-Aid and typically have the following composition.

→ Backing: The backing is often an aluminized polyester film.
→ Drug Reservoir: The drug reservoir commonly includes the active ingredient and a vehicle such as mineral oil, polyisobutylene, silicone or ethanol.
→ Control Membrane: The control membrane may be microporus polypropylene or an ethylene/vinyl acetate copolymer.
→ Protective Liner: The contact adhesive may contain mineral oil or a hypoallergenic silicone adhesive.

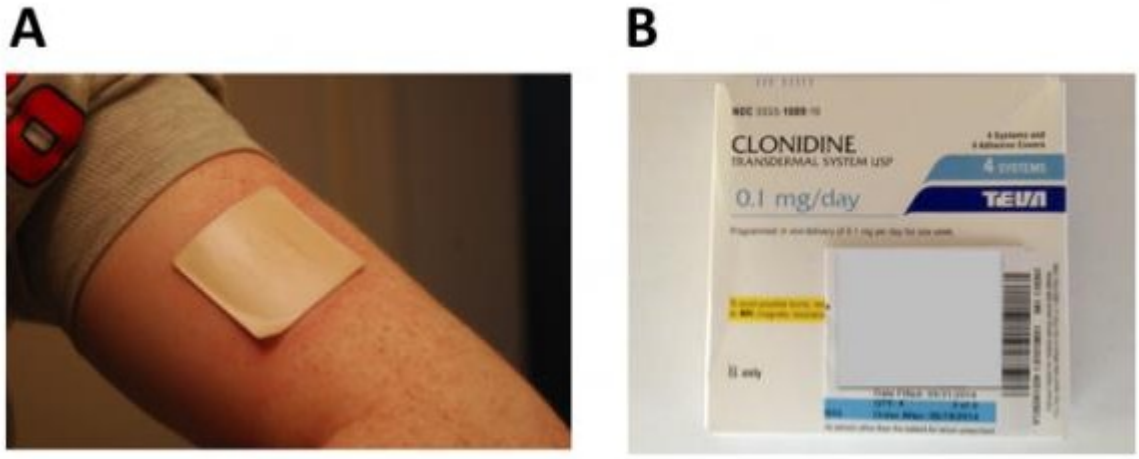

Figure 1.7. Transdermal patches. A) Nicoderm transdermal patch. From Wikipedia Commons.

Clonidine transdermal patch. This formulation is increasingly popular because: it reduces the number of doses required to only once a day (e.g. nicoderm® patch), or once a week (e.g. Ortho Evra ® contraceptive patch or the clonidine patch shown above. It doesn't require ingestion of the drug, this bypasses gastrointestinal absorption and potential first-pass metabolism. It provides a zero-order rate of delivery of drug to maintain a stable plasma concentration. It is convenient - thus better compliance. Formulations that have been developed include:

- Catapres-TTS ®: clonidine patch for hypertension
- Climara Pro ®: estrogen plus progestin contraceptive
- Duragesic ®: fentanyl patch for pain management
- Nicoderm ®: nicotine patch for smoking cessation
- Transderm Nitro: nitroglycerin patch for angina pectoris
- Transderm Scop: scopolamine patch for motion sickness

Liquid Dosage Forms

Most patients (ESPECIALLY CHILDREN) find liquid medications easier to take than solid dosage forms. Children under the age of ~10 years old commonly cannot swallow tablets, and dislike injections! However, taste can be a problem with liquid dosage forms of many medications (necessitating the addition of flavored additives).

Aqueous

→ Solutions – the most accurate way to give a variable dosage (i.e., the physician can easily adjust the dosage to the patient and the condition). Color and flavor can be used to enhance acceptance.
→ Syrups - have a sweetened taste to increase palatability, often use cherry or chocolate to mask unpleasant taste.
→ Lotions - emulsions for external application. Used to protect skin or to facilitate healing.
→ Suspensions - liquid preparations with insoluble substances for internal use (e.g., magnesium hydroxide).

Alcoholic

→ Fluid extract - in which 1 ml represents the extractable ingredients for 1 g of a plant-derived drug (e.g., St John's Wort liquid extract).
→ Tincture - in which 10 ml represents the extractable ingredients from 1 g of crude drug (e.g., tincture of belladonna). Tinctures have an ethanol percentage of at least 25–90% (50–180 US proof) (Wikipedia).
→ Elixir - active ingredient dissolved in a solution that contains 15 to 50% by volume of ethanol (e.g., phenobarbital elixir).

Miscellaneous Uses

Direct application to surface of the body or mucous membrane for local or systemic effect (i.e., eye drops, nose drops or ear drops).

→ Systemic absorption may be either desirable or not.
→ Toxicity of the liquid is important (i.e., stinging effect will greatly decrease compliance).
→ Injections must be sterile and nonpyrogenic. They also require syringes, needles and some skill in administration.

Gaseous form

The two most common medical indications for using inhalation as a route of drug administration are for the treatment of asthma or chronic obstructive pulmonary disease (COPD) using β-2 bronchodilators, anticholinergics or corticosteroids (Fanta, 2014; Stoller, 2014). In this case inhalation can be thought of as a form of topical application delivered into the lung.

Inhalation has also been used for antibiotic treatment of lung infections in patients suffering from cystic fibrosis (Fiel, 2014; Simon 2014) and is being investigated as an effective means of systemically administration of insulin in diabetics (Afrezza ®).

Smoking has served as a mechanism for delivery of nicotine from tobacco and multiple types of psychoactive drugs of abuse (e.g. marijuana, cocaine, methamphetamine, peyote & opium).

Sterile products

Sterile products" refers to products that are going to be administered using an enteral route of administration. The "products" are going to be infused directly into the bloodstream or body tissue, it is extremely important they be "sterile". For example. Consider that when a patient takes a tablet orally, their digestive system (acting as part of the immune system) has the opportunity to identify and kill any bacteria that may have hitched a ride on the tab. With a parenteral route of administration, if any contaminants are present they go right into the blood stream, bypassing the digestive system. This is why we must use a HEPA filtered flow hood preparing them. (and why we call them Sterile Product

Novel drug delivery system

The method by which a drug is delivered can have a significant effect on its efficacy. Some drugs have an optimum concentration range within which maximum benefit is derived, and concentrations above or below this range can be toxic or produce no therapeutic benefit at all. On the other hand, the very slow progress in the efficacy of the treatment of severe diseases, has suggested a growing need for a multidisciplinary approach to the delivery of therapeutics to targets in tissues. From this, new ideas on controlling the pharmacokinetics, pharmacodynamics, non-specific toxicity, immunogenicity, biorecognition, and efficacy of drugs were generated. These new strategies, often called drug delivery systems (DDS), are based on interdisciplinary approaches that combine polymer science, pharmaceutics, bioconjugate chemistry, and molecular biology.

Drug Delivery Carriers

Colloidal drug carrier systems such as micellar solutions, vesicle and liquid crystal dispersions, as well as nanoparticle dispersions consisting of small particles of 10–400 nm diameter show great promise as drug delivery systems. When developing these formulations, the goal is to obtain systems with optimized drug loading and release properties, long shelf-life and low toxicity. The incorporated drug participates in the microstructure of the system, and may even influence it due to molecular interactions, especially if the drug possesses amphiphilic and/or mesogenic properties.

a) MICELLES:

Micelles formed by self-assembly of amphiphilic block copolymers (5-50 nm) in aqueous solutions are of great interest for drug delivery applications. The drugs can be physically entrapped in the core of block copolymer micelles and transported at concentrations that can exceed their intrinsic water- solubility. Moreover, the hydrophilic blocks can form hydrogen bonds with the aqueous surroundings and form a tight shell around the micellar core. As a result, the contents of the hydrophobic core are effectively protected against hydrolysis and enzymatic degradation. In addition, the corona may prevent recognition by the reticuloendothelial system and therefore preliminary elimination of the micelles from the bloodstream. A final feature that makes amphiphilic block copolymers attractive for drug delivery applications is the fact that their chemical composition, total molecular weight and block length ratios can be easily changed, which allows control of the size and morphology of the micelles. Functionalization of block copolymers with cross linkable groups can increase the stability of the corresponding micelles and improve their temporal control. Substitution of block copolymer micelles with specific ligands is a very promising strategy to a broader range of sites of activity with a much higher selectivity.

b) LIPOSOMES:

Liposomes are a form of vesicles that consist either of many, few or just one phospholipid bilayers. The polar character of the liposomal core enables polar drug molecules to be encapsulated. Amphiphilic and lipophilic molecules are solubilized within the phospholipid bilayer according to their affinity towards the phospholipids. Participation of nonionic surfactants instead of phospholipids in the bilayer formation results in niosomes. Channel proteins can be incorporated without loss of their activity within the hydrophobic domain of vesicle membranes, acting as a size-selective filter, only allowing passive diffusion of small solutes such as ions, nutrients and antibiotics. Thus, drugs that are encapsulated in a nanocage-functionalized with channel proteins are effectively protected from premature degradation by proteolytic enzymes. The drug molecule, however, is able to diffuse through the channel, driven by the concentration difference between the interior and the exterior of the nanocage.

c) DENDRIMERS:

Dendrimers are nanometre-sized, highly branched and monodisperse macromolecules with symmetrical architecture. They consist of a central core, branching units and terminal functional groups. The core together with the internal units, determine the environment of the nanocavities and consequently their solubilizing properties, whereas the external groups the solubility and chemical behaviour of these polymers. Targeting effectiveness is affected by attaching targeting ligands at the external surface of dendrimers, while their stability and protection from the Mononuclear Phagocyte System (MPS) is being achieved by functionalization of the dendrimers with polyethylene glycol chains (PEG).

d) LIQUID CRYSTALS:

Liquid Crystals combine the properties of both liquid and solid states. They can be made to form different geometries, with alternative polar and non-polar layers (i.e., a lamellar phase) where aqueous drug solutions can be included.

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e) NANOPARTICLES:

Nanoparticles (including nanospheres and Nano capsules of size 10-200 nm) are in the solid state and are either amorphous or crystalline. They are able to adsorb and/or encapsulate a drug, thus protecting it against chemical and enzymatic degradation. Nano capsules are vesicular systems in which the drug is confined to a cavity surrounded by a unique polymer membrane, while nanospheres are matrix systems in which the drug is physically and uniformly dispersed. Nanoparticles as drug carriers can be formed from both biodegradable polymers and non-biodegradable polymers. In recent years, biodegradable polymeric nanoparticles have attracted considerable attention as potential drug delivery devices in view of their applications in the controlled release of drugs, in targeting particular organs / tissues, as carriers of DNA in gene therapy, and in their ability to deliver proteins, peptides and genes through the peroral route.

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UNIT – II Sources of drugs and their action– SMB203

II. Sources of drugs and their action

Source of drugs

1. Natural

-Plants : Leaf, Bark, Fruit, Seed

-Animals

-Microorganisms

-Mineral

2. Synthetic

-Semi-synthetic

-Synthetic Sources of Drugs

Before the twentieth century, drugs used for the treatment of diseases were obtained from natural sources like plants, animals, microorganisms, and minerals, and among them, plants were the major source of natural drugs. At present, most of the drugs are obtained from synthetic and biosynthetic sources. The nature was once served as the source of all medicaments and plants, especially the higher plants have been continuing the service since antiquity as important sources of novel compounds useful directly as medicinal agents, as model compounds for synthetic or semi-synthetic structure modifications and optimization, as biochemical and/or pharmacological probes, and as sources of inspiration for generations of synthetic organic medicinal chemists. Plant-derived compounds which have recently undergone development include the anti-cancer agents, taxol and camptothecin, the Chinese antimalarial drug, artemisinin, and the East Indian Ayurvedic drug, forskolin. These and many other examples serve to illustrate the continuing value of plant-derived secondary metabolites as viable compounds for modern drug development (Newman et al. 2003; Newman and Cragg 2007). Natural sources are most primitive and abundant. Drugs obtained from the natural sources include a. Plant, b. Animal, c. Microbial, d. Marine, e. Mineral, and f. Geographical sources. Plant, Animal, Microbial and Marine may be put under common heads—the biological sources.

Biological sources are comprised of Monera, Protista, Animalia, Plantae, and Fungi —the 5 kingdoms of Whittaker (1969).

Plant, Animal, and Microbial Sources

The entire plant, plant parts, secretion and exudate of plants are the sources of plant drugs. Ergot, ephedra, and datura are entire plants, senna leaf and pod pods, leaf of Digitalis (cardiotonic digoxin), bark of Chinhona (antimalarial quinine), capsule of Opium (analgesic morphine), seeds of Nux vomica, seeds of Eserin (anti-cholinestrase serine-physostigmine), rhizome of ginger function as sources of a number of drugs useful against different diseases. Though in few cases, as in lemon and orange peels and in colchicum corm, drugs are used in fresh condition, and most of the drugs are dried after collection. Crude drugs may also be obtained by simple physical processes like drying or extraction with water. Thus, the aloe is dried juice of leaves of aloe species, opium is the dried latex from poppy capsules, and black catechu is the dried aqueous extract from the wood of Acacia catechu. Further, drugs used by doctors or pharmacists, directly or indirectly, like cotton, silk, jute, nylon in surgical dressings or kaolin; diatomite used for filtration of turbid liquids; or gums, wax, gelatin, agar used as pharmaceutical auxiliaries or flavoring or sweetening agents or drugs used as vehicles or insecticides are treated in pharmacognosy. Plants have always been a rich source of pharmalogical active principles (lead compounds) like alkaloids, glycosides, oils, resins, gums, tannins, and much more.

Alkaloids

Include a vast group of chemical compounds including atropine from Atropa belladonna, Jimson from *Datura stramonium*, morphine from *P. somniferum*, caffeine from Coffee, Tea,

Cocoa, cocaine from *Erythroxylum coca*, digitalis from *Digitalis purpurea*, digoxin from *Digitalis lanata*, quinine from *Cinchona pubescens*, reserpine from *Rauvolfia serpentine*, tubocurarine from *Chondrodendron tomentosum*, nicotine from *Nicotina tobacum*, and muscarine from mushroom of Inocybe and Clitocybe spp.). Many of these lead compounds are useful drugs in themselves (e.g. alkaloids, morphine and quinine), and others have been the basis for synthetic drugs (e.g. local anaesthetics developed from cocaine). Psilocin, berberine, vincristine, galantamine, vincamine, quinidine, ephedrine etc. are some other alkaloids.

Terpenes and Terpenoids

Ginkgo, ginseng, valerian, Melissa officinalis, sage; azadirachtin, (Neem tree), artemisinin, present in Artemisia annua Chinese worm wood and tetrahydrocannabinol, present in Cannabis sp.

Glycosides

They are the combination of sugar moiety (glucone) with non-sugar moiety (aglycone). Sugar moiety is not essential for the pharmacological activity but it governs the pharmacokinetic properties of the glycoside. Pharmacological activity resides in the non-sugar aglycone moiety. Some examples are digitoxin, digoxin, and ouabain.

Cyanogenic glycosides (nitrogen-containing) include amygdalin, dhurrin, linamarin, lotaustralin, prunasin, etc.

Oils

They are liquids and insoluble in water. Essential, fixed, and mineral oils are the three main categories of oils, and they are used for various medicinal purposes. Essential oils (or volatile oils)—an essential oil is a concentrated hydrophobic liquid containing volatile aroma compounds from plants and leaves no stains on evaporation. Examples of essential oils are clove oil, peppermint oil, eucalyptus oil, and ginger oil. Essential oils are subdivided into hydrocarbons (terpenes—monoterpenes, sesquiterpenes, diterpenes, etc.) and the oxygenated compounds (esters, aldehydes, ketones, alcohols, phenols, oxides, etc.). These compounds are found in the oils extracted from leaf, bud, flower parts, fruit, seed, wood, bark, and other plant parts angiosperms like anise, coriander, peppermint, rosemary, sandalwood, cinnamon, lemon, caraway, dill, clove, eucalyptus, nutmeg, camphor, and conifers like pine, fir, spruce, and juniper. Terpenes are anti-viral, anti-bacterial, anti-septic and anti-inflammatory and contain active principles like caryophyllene and valencene, chamazulene, farnesol, chamazulene, farnesene limonene, pinene camphene, cadinene, cedrene, dipentene, phellandrene, terpinene, sabinene, and myrcene. Linalyl acetate, geraniol acetate, bornyl acetate, eugenol acetate, and lavendulyl acetate are some common esters and may be found in bergamot, Clary sage, lavender, sweet marjoram, and others. Ester compounds are anti- fungal, calming and relaxing. Citral, citronellal, benzaldehyde, cinnamic aldehyde, cuminic aldehyde, and perillaldehyde are some of the examples of aldehyde compounds present in essential oils. They are found in the oils of melissa, also known as lemon balm, balm or balm mint (Melissa officinalis), lemongrass, lemon, mandarin, lemon-scented eucalyptus, and citronella. Aldehyde compounds of the essential oil have very distinctive anti-septic and anti- viral activities. They can be applied topically or inhaled. Ketones include thujone, jasmine, fenchone, camphor, carvone, menthone, methyl nonyl ketone, and pinacamphone and are largely found in oils used for the upper respiratory system. They are helpful in the treatment of dry asthma, colds, flu, and dry cough. Terpenealkohols include linalool, citronellol, geraniol, farnesol, borneol, menthol, nerol, terpineol, vetiverol, benzyl alcohol, bisabolol, and cedrol. These alcohols are anti-inflammatory, anti-bacterial, anti-mycotic, and ulcer- protective and can help relieve discomfort. They may be found in rosewood, lavender, rose, lemon, eucalyptus, geranium,

palmarosa, and others. Eugenol, thymo, lcarvacrol, methyl eugenol, methyl chavicolanethole, safrole, myristicin, apiol etc. are phenols present in essential oils. Phenols are responsible for the fragrance of oil and have antiseptic and anti- bacterial properties. These phenol compounds are found in clove, thyme, cinnamon, and other essential oils. Researchers believe it may possibly contain some anti-cancerous properties. Oxides of essential oil include cineol (or eucalyptol), linalol oxide, ascaridol, bisabolol oxide, and bisabolone oxide. Cineol is by far the most important member of the oxide family and is the principal constituent of eucalyptus oil. It may also be found in rosemary, cinnamon, melissa, basil, and ravensara. It is used as an anesthetic and antiseptic, and works as an expectorant. All pure essential oils have some anti-bacterial properties. They increase the production of white blood cells, which help fight infectious illnesses. It is through these properties that aromatic herbs have been esteemed so highly throughout the ages and so widely used during the onsets of malaria, typhoid, and of course, the epidemic plagues during the sixteenth century. Research has found that people who consistently use pure essential oils have a higher level of resistance to illnesses, colds, flues, and diseases than the average person. Further indications show that such individuals, after contracting a cold, flu, or other illness, will recover 60–70% faster than those who do not use essential oils. Fixed oils are esters of glycerin with fatty acids of high molecular weight, particularly palmitic, stearic, and oleic acids. Simple esters of glycerin are often called glycerides. The relative proportion of liquid or solid ester of glycerin due to fatty acid chain length and its degree of saturation determine the difference in consistency between oils and fats. The oils contain a greater proportion of liquid glycerides (polyunsaturated glycerinoleate), while fats are rich in solid glycerides (glycerin stearate). Fixed oils and volatile oils differ from each other in that the volatile oils contain no glycerin esters. Fixed oils may be of vegetable origin, from fruits and seeds of oil yielding plants, e.g., olive oil, mustard oil, castor oil, croton oil, peanut oil, etc. (fatty oil); coconut oil, palm oil (soft fats), or of animal origin, e.g., cod liver oil, shark liver oil, lard (hard fats), carnaiiba wax, and beeswax (harder vegetable and animal wax). Arachis, Castor, Chaulmoogra, Coconut, Cottonseed, Linseed, Olive, Sesame, Almond also yield fixed oils. They are non-volatile and leave greasy stains on evaporation. They have caloric or food value. They form soaps with alkalies. On prolonged stay, they become rancid. They do not have marked pharmacological activity and have little pharmacological use except castor oil (purgative) or a rachis oil (demulcent). Olive oil, a monounsaturated fat, and the polyunsaturated omega-3 fats from fish and flaxseed oils are able to relieve suffering from arthritis to cancer. Vegetable fats, e.g., margarine, safflower oil, and animal fats, e.g., butter, lard are almost equally responsible for increasing blood cholesterol level and risk of heart disease and also increase the risk of cancer. Mineral oil—a mineral oil is any of various colorless, odorless, light mixtures of higher alkanes from a mineral source, particularly a distillate of petroleum. The name mineral oil by itself is imprecise and includes white oil, liquid paraffin, pariffinumliquidum, and liquid petroleum. And on the basis of their various consistencies, they are grouped as hard paraffin, soft paraffin, and liquid paraffin. Hard and soft paraffin are used as vehicles for the preparation of ointments while liquid paraffin is employed as a purgative. Baby oil is a perfumed mineral oil. Mineral oils may be used in cell culture (as an overlay covering microdrops of culture medium in petridishes during the culture of oocytes and embryos), poultry (when chickens infected with scaly mites on the shank, toes, and webs), veterinary (in vaccines as an adjuvant to stimulate a cell-mediated immune response to the vaccinating agent), and cosmetics (as common ingredient in baby lotions, cold creams, ointments, and other cosmetics).

Steroids

Terpenes with a particular ring structure. Saponins—plant steroids, often glycosylated. Phenolic compounds include curcumin, resveratrol, epigallocatechin-3-gallate, soyisoflavones.

Gums

Gums and mucilageare polysaccharide hydrocolloids of plant origin and yield mixture of sugars and uronic acids on hydrolysis. Gums are considered to be pathological products, formed by giving injury to the plant or due to unfavorable conditions (drought other stresses) by the breakdown of cell walls (extra cellular formation). Mucilages are generally normal physiological metabolites, formed within the cell (intracellular formation). Gums readily dissolve in water, whereas mucilage forms slimy masses. Natural gums can be classified according to their origin and also as uncharged or ionic polymers (polyelectrolytes). Natural gums may be obtained from seaweeds (polyelectrolytes—agar, alginic acid, sodium alginate, carrageenan, laminarin, etc.); higher plants (polyelectrolytes—gum arabic from Acacia trees, gum ghatti from Anogeissus trees, gum tragacanth from Astragalus shrubs, Karaya gum from Sterculia trees, etc.; uncharged—guar gum from guar beans, Abelmoschus gum from the fresh fruits of Abelmoschusesculentus, locust bean gum from the seeds of Ceratoniasiliqua, b-glucan from oat or barley bran, chicle gum obtained from the Chicle tree, dammar gum from the Dipterocarpaceae trees, glucomannan from Konjac plant, Mastic gum from Mastic tree, Psyllium seed husks from the Plantago plant, spruce gum from Spruce trees, tara gum from the seeds of tara tree). Natural gums may also be produced by bacterial fermentation (polyelectrolytes—gellan gum and uncharged—xanthan gum). Mucilage is obtained from the seeds of *Trigonella foenum-graceum*. In the food industry, they are used as thickening agents, gelling agents, emulsifying agents, and stabilizers. In other industries, they are also used as adhesives, binding agents, crystal inhibitors, clarifying agents, encapsulating agents, flocculating agents, swelling agents, foam stabilizers, etc. A large number of gums are used as pharmaceutical excipient as diluent, binder, disintegrant in tablets, thickeners in oral liquids, protective colloids in suspensions, gelling agents in gels, and bases in suppository. Gut agar and psyllium seed gums act as hydrophilic colloids and function as bulk purgatives. Gum acacia and gum tragacanth are used as suspending agents in making emulsions and mixtures. The mucilage (mannose, galactose, and xylose) obtained from fenugreek was found to be better release retardant compared to hypromellose at equivalent content. Mucilage from fresh leaves of Hibiscus rosa-sinensis (L-rhamnose, D-galactose, D-galacturonic acid, and D- glucuronic acid) is used for the development of sustained release tablet has been reported. Aloe mucilage from the leaves of Aloe barbadensis contains arabinan, arabinorhamnogalactan, galactan, galactogalacturan, glucogalactomannan, galactoglucoarabinomannan, glucuronic acid, etc. A controlled delivery system of glibenclamide using aloe mucilage proved that Aloe mucilage can be used as a matrix forming material for making controlled release glibenclamide matrix tablets.

Resin

Resin in is a polymer hydrocarbon secretion of many plants, particularly coniferous trees. It is distinct from cell sap, latex, gum, or mucilage. They are produced by oxidation and polymerization of volatile oils. Natural resins are typically fusible and flammable organic substances that are transparent or translucent and are yellowish to brown in color; insoluble in water but soluble in alcohol, chloroform, and ether. Asafoetida, Benzoin, Colophony, Copaiba, Guaiacum, Guggal, Mastic, Myrrh, Peru Balsam, Sandarac, Storax, Tolu Balsam, Tar, Coal Tar oleoresins (aspidium); gum resins (asafoetida); oleogum resin (myrrh); balsams (benzoin, tolu, peru); benzoin shellac, podophyllum, etc. are some of the common examples of resin. They may combine with oil, mucilage, and gum. Benzoin is

used as inhalation in common cold, tincture benzoin is applied as antiseptic protective sealing over bruises, colophony (an oleoresin) is used as an ingredient in various plasters, shellac (from Lucifer lacca) is used for enteric coating of tablets, balsams are used in the treatment of cough and bronchitis for their antiseptic and protective properties, and podophyllum is used as an irritant purgative.

Tannins

Tannins are astringent, bitter, non-nitrogenous, polyphenolic plant constituents. Tannin binds to and precipitates proteins and various other organic compounds including amino acids and alkaloids. Tannins are common in fruits (grapes, persimmon, blueberry, etc.), in tea, in chocolate, in legume forages (trefoil, etc.), in legume trees (Acacia spp., Sesbania spp., etc.), in grasses (sorghum, corn, etc.). Other important tannin-containing plants are Quercus sp. (oak), Acer sp. (maple), Betulasp. (birch), Salix caprea (willow), Pinus sp. (Pine), Sorghum sp. Pyrogallol tannins are glycosides of glucose that occur in oak galls. Pyrocatechol tannins are sugar-free derivatives of catechol that are present in catechu and eucalyptus. Tannic acid is tannin that is obtained from oak galls and is used for treating burns and diarrhea.

Toxins

Toxins-Botulinum toxin from Clostridium botulinum prevent cholinergic transmission and could well prove a lead for the development of novel anticholinergic drugs.

Animal sources

Drugs obtained from animals sources are (i) whole animals, (ii) their organs, and (iii) glandular products (thyroid organ) and extract (liver), etc. Whole animals include European medicinal leech Hirudomedicinalis, Mexican medical leech Hirudomanillensis (hirudin, heparin), cantharides-skin irritants (form Mylabrissp and L. vesicatoria-Spanish fly, the blistering beetles of Coleoptera), lac or shellac (the resinous substance prepared from a secretion of the insect-lac bug, Lacciferlacca), musk scent (the dried secretion from the preputial follicles of the musk deer, Moschusmoschiferus), civet (the secretion obtained from the perineal follicles of civet cats, Viverra spp.), chalk (finely powdered whitish or grayish rock), which consists mainly of the shells of unicellular microorganisms, Foraminifera (amoeboid protists) and coccolithophores; (ii) different organs and their products include skin of the African clawed frog Xenopuslaevis (antibiotic peptides), skin extracts of the Ecuadorian poison frog Ameeregabilinguis (potent analgesic compound epibatidine), pancreas of cow and pork (insulin, hormone), cow stomach (pepsin), thyroid gland (thyroxin), liver (liver extract, vit. B12), cod liver oil (from Gadus spp., mainly from the Atlantic cod Gadusmorhua), pregnant woman (human chorionic gonadotropin-HCG hormone), post menopausal woman urine (menotrphin), human kidney cells (urokinase), antitoxic sera, etc. are some of the animal sources for many valuable drugs as well as halibut-liver oil (from Hippoglossus vulgaris), suet (hard raw beef or mutton fat), lard (pig fat), spermaceti (wax found in the head cavities of the sperm whale), wool fat (waxy substance, skin lipid, secreted by the sheep Ovisaries); and (iii) their products and extracts include venoms and toxins from snakes, spiders, scorpions, insects, etc. are polypeptides (a-bungarotoxin from cobras) or non-peptide toxins (tetrodotoxin from the puffer fish). They have been used as lead compounds in the development of novel drugs, e.g., teprotide, a peptide from the Brazilian viper, was the lead compound for the development of the antihypertensive agents cilazapril and captopril. Gelatin (obtained by the partial hydrolysis of collagen derived from the skin, white connective tissue and bones of animals like cow hide splits, bones, pork skin, and fish skin), honey (produced bees Apis spp.), beeswax (natural wax produced in the bee hive of honey by Apis spp.), chitin (most abundant natural amino polysaccharide, next to cellulose, derived from two marine crustaceans, shrimp—

Penaeuskerathurus and crabs—Carcinusmediterraneus shells), chitosan—deacetylated chitin derivative, chondroitin sulfate (a sulfated glycosaminoglycan and an important structural component of cartilage and provides much of its resistance to compression, manufactured from cow cartilage), hyaluronic acid (non-sulfated glycosaminoglycan distributed throughout connective, epithelial, and neural tissues), animal (derived from cows, pigs pancreases and until the 1980s, animal insulin was the only treatment for insulin dependent diabetes), human chorionic gonadotropin—hCG (a hormone produced by the syncytiotrophoblast of the placenta following pregnancy of a woman), thyroxin (from sheep thyroid), pituitary gonadotropins (glycoprotein hormones secreted by gonadotropic cells of the anterior pituitary, used in fertility medication), heparin (an anticoagulant), vaccines (live attenuated viruses—rubella, measles, oral polio, mumps; or bacteria—bacillus calmette-guerin, BCG; inactivated viruses—parenteral polio, hepatitis A; or parts of the virus—pneumococcal vaccine, influenza; inactivated bacterial toxins—diphtheria and tetanus; genetically engineered—hepatitis B vaccine by inserting a segment of the viral gene in a yeast cell); sera (antidiphtheria, antitetanus sera from horse and sheep); etc.

Microbial sources

Many life-saving drugs are obtained from microbes such as penicillin from Penicillium notatum, chloramphenicol from Streptomyces venezuelace, anti-fungal drug grisofulvin from Penicilliumgriseofullivum, neomycin from Streptomyces fradiae and streptomycin from actinobacterium Streptomyces griseus. Aminoglycosides such as gentamicin and tobramycin are obtained from Micromonospora sp. and Streptomyces tenebrarius, respectively; xanthan (polysaccharide gum secreted by Xanthomonascampestris, composed of repeat units of glucose, mannose, and glucuronic acid in the molar ratio 2:2:1), dextran (polysaccharide of glucose synthesized by lactic acid bacteria Leuconostocmesenteroides, Streptococcus mutans, Lactobacillus brevis), curdian (b-1,3- glucan polymer, product of Agrobacterium biobar and Alcaligenesfaecalis), pullulan (a polysaccharide polymer of maltotriose units produced from starch by the fungus Aureobasidium pullulans), emulsan (a polyanionicheteropolysaccharidebioemulsifier produced by Acinetobactercalcoaceticus RAG-1.), baker's yeast glycan (polysaccharide derived from ruptured yeast cell walls of Saccharomyces cerevisiae), schizophyllan (a neutral extracellular polysaccharide produced by the fungus Schizophyllum commune), lentinanan (intravenous anti-tumor polysaccharide isolated from the fruit body of an edible mushroom shiitake—Lentinula edodes), krestin, or polysaccharide-K—PSK (a protein-bound polysaccharide, an anti-cancer immunologic adjuvant, from the mushroom fruitbody of Trametes versicolor), and scleroglucana (water-soluble polysaccharide produced by fermentation of the filamentous fungus Sclerotiumrolfsii). Microbial metabolites other than antibiotic are also known, e.g., asperlicin (a novel antagonist of a peptide hormone, cholecystokinin—CCK) from Aspergillus alliaceus, lovastatin from oyster mushrooms—Pleurotusostreatus and Chinese red yeast rice—Monascuspurpureus

Marine Sources

Coral, sponges, fish, and marine microorganisms have a wealth of biologically potent chemicals with interesting inflammatory, anti-viral, and anticancer activity. For example, curacin A, lipid constituent, from a marine cyanobacterium Lyngbya majuscule shows potent anti-tumor activity. Other anti-tumor agents derived from marine sources include eleutherobin from coral Eleutherobia sp., discodermolide from the Caribbean marine sponge Discodermiadissoluta, bryostatins from colonial marine animal of North Carolina Bugula neritina, dolostatins from small marine gastropod molluskDolabellaauricularia, and cephalostatinsa, a broad class of bactericidal antibiotics from Cephalosporiumacremonium fungus.

Mineral (Metallic and Non-metallic) Sources

Drugs from mineral source are kaolin, chalk, diatomite and many more. Minerals or their salts are useful pharmacotherapeutic agents. For example, ferrous sulfate (FeSO4) is used in iron deficiency anemia, magnesium sulfate (MgSO4) is employed as purgative, magnesium trisilicate, aluminium hydroxide {Al(OH)3} and sodium bicarbonate (NaHCO3) are used as antacids for hyperacidity and peptic ulcer, zinc oxide ointment as sunscreen, skin protectant, in wounds and in eczema, gold salts (solganal, auranofin) as anti-inflammatory and in rheumatoid arthritis, bentonite (absorbent aluminium phyllosilicate clay), talc (hydrated magnesium silicate). Kaolin (aluminium silicate) is used as an adsorbent in antidiarrheal mixtures, mercurial salts are used in syphilis andiodine is used as antiseptic. Borax and fluorine have antiseptic properties, selenium as selenium sulfide is used in anti-dandruff shampoos and petroleum is used in the preparation of liquid paraffin. Radioactive isotopes of iodine, phosphorus, gold are employed for the diagnosis/treatment of diseases particularly malignant conditions. Kiesselguhr, the fossilized remains of diatoms, is a form of silica composed of the siliceous shells of diatoms. 4.2.3 Geographical or Habitat Sources Geographical source or habitat gives us information about the country or place where the drug is produced. Zingiberofficinale is indigenous to southern China and was spread eventually to the Spice Islands (Maluku province of Indonesian), other parts of Asia and subsequently to West Africa and the Caribbean and Cannabis indica, Tamarinds indica, Strychnosnux-vomica and Plantagoispaghula in the Indian subcontinent. In some cases, the original native place of a drug is not the same as the present geographical source, e.g., cinchona is a native of South America and is at present cultivated in Indonesia, India, and Congo.

Pharmacodynamics

Pharmacodynamics (PD) is the study of the biochemical and physiologic effects of drugs (especially pharmaceutical drugs). The effects can include those manifested within animals (including humans), microorganisms, or combinations of organisms (for example, infection).Pharmacodynamics and pharmacokinetics are the main branches of pharmacology, being itself a topic of biology interested in the study of the interactions between both endogenous and exogenous chemical substances with living organisms.In particular, pharmacodynamics is the study of how a drug affects an organism, whereas pharmacokinetics is the study of how the organism affects the drug. Both together influence dosing, benefit, and adverse effects. Pharmacodynamics is sometimes abbreviated as PD and pharmacokinetics as PK, especially in combined reference (for example, when speaking of PK/PD models).

Pharmacodynamics places particular emphasis on dose–response relationships, that is, the relationships between drug concentration and effect. One dominant example is drug-receptor interactions as modeled by L + R <=> LR

where L, R, and LR represent ligand (drug), receptor, and ligand-receptor complex concentrations, respectively. This equation represents a simplified model of reaction dynamics that can be studied mathematically through tools such as free energy maps.

Drug action mechanism

In pharmacology, the term mechanism of action (MOA) refers to the specific biochemical interaction through which a drug substance produces its pharmacological effect. A mechanism of action usually includes mention of the specific molecular targets to which the drug binds, such as an enzyme or receptor. Receptor sites have specific affinities for drugs based on the chemical structure of the drug, as well as the specific action that occurs there.

Drugs that do not bind to receptors produce their corresponding therapeutic effect by simply interacting with chemical or physical properties in the body. Common examples of drugs that work in this way are antacids and laxatives. In contrast, a mode of action (MoA) describes functional or anatomical changes, at the cellular level, resulting from the exposure of a living organism to a substance.

Pharmacodynamics is the study of the biochemical and physiologic effects of drugs and their mechanisms of action on the body or on microorganisms and other parasites within or on the body. It considers both drug action, which refers to the initial consequence of a drug- receptor interaction, and drug effect, which refers to the subsequent effects. The drug action of digoxin, for example, is inhibition of membrane Na+/K+-ATPase; the drug effect is augmentation of cardiac contractility. In this example, the clinical response might comprise improved exercise tolerance.

Not all drugs exert their pharmacologic actions via receptor-mediated mechanisms. The action of some drugs—including inhalation anesthetic agents, osmotic diuretics, purgatives, antiseptics, antacids, chelating agents, and urinary acidifying and alkalinizing agents—is attributed to their chemical action or physicochemical properties. Certain cancer and antiviral chemotherapeutic agents, which are analogues of pyrimidine and purine bases, elicit their effects when they are incorporated into nucleic acids and serve as substrates for DNA or RNA synthesis. The effect of most drugs, however, results from their interactions with receptors. These interactions and the resulting conformational changes in the receptor initiate biochemical and physiologic changes that characterize the drug's response.

Drug Concentration and Effect

Drug therapy is intended to result in a particular pharmacologic response of desired intensity and duration while avoiding adverse drug reactions. The relationship between the administered dose and the clinical response has been investigated for some drugs using a pharmacokinetic/pharmacodynamic (PK/PD) modeling approach, which is generally based on the plasma concentration-response relationship. For other drugs, a simpler relationship between the concentration and effect in an idealized in vitro system is modeled mathematically to conceptualize receptor occupancy and drug response. The model assumes that the drug interacts reversibly with its receptor and produces an effect proportional to the number of receptors occupied, up to a maximal effect when all receptors are occupied. The reaction scheme for the model is:

$$\text{Drug (D)} + \text{Receptor (R)} \underset{k_1}{\overset{k_2}{\leftrightarrow}} \text{DR} \rightarrow \text{Effect}$$

in which k2 and k1 are rate constants.

The relationship between effect and the concentration of free drug for the model is given by the Hill equation, which can be written as:

$$E = \frac{E_{max} \times C_n}{EC_{50} + C_n}$$

in which E is the effect observed at concentration C, Emax is the maximal response that can be produced by the drug (efficacy), EC50 is the concentration of drug that produces 50% of maximal effect (potency), and the Hill coefficient n is the slope of the log10 concentration-effect relationship (sensitivity).

The above equation describes a rectangular hyperbola when response (y-axis) is plotted against concentration (x-axis). However, dose- or concentration-response data is generally plotted as drug effect (y-axis) against log10 dose or concentration (x-axis). The transformation yields a sigmoidal curve that allows the potency of different drugs to be

readily compared. In addition, the effect of drugs used at therapeutic concentrations commonly falls on the portion of the sigmoidal curve that is approximately linear, ie, between 20% and 80% of maximal effect. This makes for easier interpretation of the plotted data.

Agonists and Antagonists

An agonist is a drug that binds to receptors and thereby alters (stabilizes) the proportion of receptors in the active conformation, resulting in a biologic response. A full agonist results in a maximal response by occupying all or a fraction of receptors. A partial agonist results in less than a maximal response even when the drug occupies all of the receptors.

There are four types of drug antagonism. Chemical antagonism involves chemical interaction between a drug and either a chemical or another drug leading to a reduced or nil response. Physiologic antagonism occurs when two drugs acting on different receptors and pathways exert opposing actions on the same physiologic system. Pharmacokinetic antagonism is the result of one drug suppressing the effect of a second drug by reducing its absorption, altering its distribution, or increasing its rate of elimination. Pharmacologic antagonism occurs when the antagonist inhibits the effect of a full or partial agonist by acting on the same pathway but not necessarily on the same receptor.

Pharmacologic antagonists comprise three subcategories. A reversible competitive antagonist results in inhibition that can be overcome by increasing the concentration of agonist. The presence of a reversible competitive antagonist causes a parallel rightward shift of the log concentration-effect curve of the agonist without altering Emax or EC50. An irreversible competitive antagonist also involves competition between agonist and antagonist for the same receptors, but stronger binding forces prevent the effect of the antagonist being fully reversed, even at high agonist concentrations. The presence of an irreversible competitive antagonist causes a rightward shift of the log concentration-effect curve of the agonist that generally displays decreased slope and reduced maximum effect. A noncompetitive antagonist inhibits agonist activity by blocking one of the sequential reactions between receptor activation and the pharmacologic response. Noncompetitive antagonism is generally reversible but can be irreversible. Noncompetitive antagonists and irreversible competitive antagonists cause similar perturbations in the log concentration-effect curve of agonists. Isolated tissue experiments are used to distinguish the two subcategories, because noncompetitive antagonists are generally reversible.

Agonists, but not antagonists, elicit an effect even when they bind to the same site on the same receptor. An explanation is provided by both structural and functional studies, which indicate that receptors exist in at least two conformations, active and inactive, and these are in equilibrium. Because agonists have a higher affinity for the receptor's active conformation, agonists drive the equilibrium to the active state, thereby activating the receptor. Conversely, antagonists have a higher affinity for the receptor's inactive conformation and push the equilibrium to the inactive state, producing no effect.

The concept of spare receptors explains a maximum response being achieved when only a fraction of the total number of receptors is occupied. For example, an action potential and maximal twitch of muscle fibers is elicited when 0.13% of the total number of receptors at a skeletal neuromuscular junction is simultaneously activated. From a functional perspective, spare receptors are significant, because they increase both the sensitivity and speed of a tissue's responsiveness to a ligand.

Structure–Activity Relationships

Structure-activity relationships are exploited in drug design, because small changes in chemical structure can produce profound changes in potency. For example, the substitution

of a proton by a methyl group accounts for codeine being ~1,000 times less potent than morphine in its action on opioid receptors.

Signal Transduction and Drug Action

Most receptors are proteins. The best characterized of these are regulatory proteins, enzymes, transport proteins, and structural proteins. Nucleic acids are also important drug receptors, particularly for cancer chemotherapeutic agents.

The receptors for several neurotransmitters modulate the opening and closing of ion channels through ligand gating or voltage gating. The nicotinic acetylcholine receptor is an example of a ligand-gated receptor; it allows Na+ to flow down its concentration gradient into cells, resulting in depolarization. Most clinically useful neuromuscular blocking drugs compete with acetylcholine for the receptor but do not initiate ion-channel opening. Other ligand-gated ion channels include the CNS receptors for the excitatory amino acids (glutamate and aspartate), the inhibitory amino acids (γ-aminobutyric acid [GABA] and glycine), and certain serotonin (5-HT3) receptors. The sodium channel receptor is an example of a voltage-gated receptor; these are present in the membranes of excitable nerve, cardiac, and skeletal muscle cells. In the resting state, the Na+/K+-ATPase pump in these cells maintains an intracellular Na+ concentration much lower than that in the extracellular environment. Membrane depolarization causes channel opening and a transient influx of Na+ ions, followed by inactivation and return to the resting state. The action of local anesthetics is due to their direct interaction with voltage-gated Na+ channels.

Many transmembrane receptors are linked to guanosine triphosphate binding proteins, which activate second messenger systems. Two important second messenger systems are cyclic adenosine monophosphate (cAMP) and the phosphoinositides. In cAMP second messenger systems, binding of the ligand to the receptor increases or decreases adenylyl cyclase activity, which in turn regulates the formation of cAMP from adenosine triphosphate. The activation of protein kinase A by cAMP results in the phosphorylation of proteins and a physiologic effect. From a therapeutic standpoint, drug binding to β-adrenergic, histamine H2, or dopamine D1 receptors activates adenylyl cyclase, whereas binding to muscarinic M2, α2-adrenergic, dopamine D2, opiate μ and δ, adenosine A1, or GABA type B receptors inhibits adenylyl cyclase. In phosphoinositide second messenger systems, membrane phosphatidylinositol 4,5-biphosphate is hydrolyzed to 1,4,5-trisphosphate (IP3) and 1,2-diacylglycerol (DAG) by activation of phospholipase
C. Both IP3 and DAG activate kinases, and in the case of IP3, this involves the mobilization of calcium from intracellular stores. The action of numerous drugs is due to their interaction with receptors that rely on these second messengers, which include α1-adrenergic, muscarinic M1 or M2, serotonin 5-HT2, and thyrotropin-releasing hormone receptors.

Protein tyrosine kinase receptors are generally transmembrane enzymes that phosphorylate proteins exclusively on tyrosine residues, rather than on serine or threonine residues. They include endocrine hormone receptors for insulin and receptors for several growth hormones.

Intracellular receptors mediate the action of hormones such as glucocorticoids, estrogen, and thyroid hormone and related drugs. The hormones, which regulate gene expression in the nucleus, are lipophilic and freely diffuse through the cell membrane to reach the receptor. Glucocorticoid receptors reside predominantly in the cytoplasm in an inactive form until they bind to the glucocorticoid steroid ligand. This results in receptor activation and translocation to the nucleus, where the receptor interacts with specific DNA sequences. Unlike glucocorticoid receptors, the receptors for estrogen and thyroid hormone reside in the nucleus.

Intracellular receptors are also important in mediating the action of antimicrobial drugs, including the penicillins, sulfonamides, trimethoprim, aminoglycosides, phenicols, macrolides, and fluoroquinolones. The mechanisms of action include inhibition of bacterial protein synthesis, inhibition of cell wall synthesis, inhibition of enzymatic activity, alteration of cell membrane permeability, and blockade of specific biochemical pathways.

Receptor-mediated mechanisms of action of several classes of anthelmintics are well understood. For example, the benzimidazoles and pro-benzimidazoles bind to nematode tubulin, preventing its polymerization during microtubular assembly and thus disrupting cell division. Depletion of ATP as the result of salicylanilides uncoupling oxidative phosphorylation and the inhibition of enzymes in the glycolytic pathway by benzene sulfonamides are other examples. Several classes of anthelmintics interfere with neurotransmission in parasites. A case in point is macrocyclic lactones, which potentiate inhibitory neurotransmission via GABA and glutamate-gated chlorine channels.

Dose response curve

The dose–response relationship, or exposure–response relationship, describes the magnitude of the response of an organism, as a function of exposure (or doses) to a stimulus or stressor (usually a chemical) after a certain exposure time.Dose–response relationships can be described by dose–response curves. This is explained further in the following sections. A stimulus response function or stimulus response curve is defined more broadly as the response from any type of stimulus, not limited to chemicals.

Regardless of how a drug effect occurs—through binding or chemical interaction—the concentration of the drug at the site of action controls the effect. However, response to concentration may be complex and is often nonlinear. The relationship between the drug dose, regardless of route used, and the drug concentration at the cellular level is even more complex (see Pharmacokinetics).

Dose-response data are typically graphed with the dose or dose function (eg, log10 dose) on the x-axis and the measured effect (response) on the y-axis. Because a drug effect is a function of dose and time, such a graph depicts the dose-response relationship independent of time. Measured effects are frequently recorded as maxima at time of peak effect or under steady-state conditions (eg, during continuous IV infusion). Drug effects may be quantified at the level of molecule, cell, tissue, organ, organ system, or organism.

A hypothetical dose-response curve has features that vary (see figure Hypothetical dose-response curve):

- Potency (location of curve along the dose axis)
- Maximal efficacy or ceiling effect (greatest attainable response)
- Slope (change in response per unit dose)

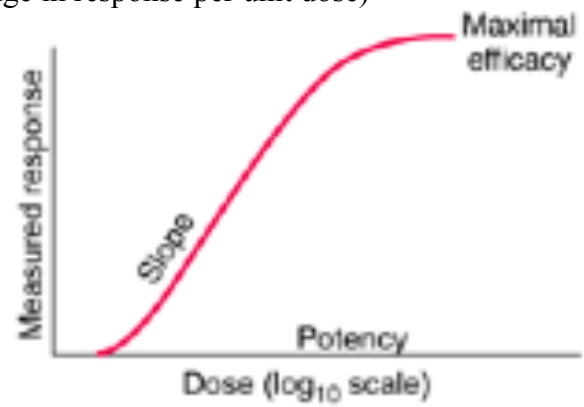


Figure 2.1. Hypothetical dose response curve

Biologic variation (variation in magnitude of response among test subjects in the same population given the same dose of drug) also occurs. Graphing dose-response curves of drugs studied under identical conditions can help compare the pharmacologic profiles of the drugs (see figure Comparison of dose-response curves for drugs X, Y, and Z). This information helps determine the dose necessary to achieve the desired effect.

Drug X has greater biologic activity per dosing equivalent and is thus more potent than drug Y or Z. Drugs X and Z have equal efficacy, indicated by their maximal attainable response (ceiling effect). Drug Y is more potent than drug Z, but its maximal efficacy is lower.

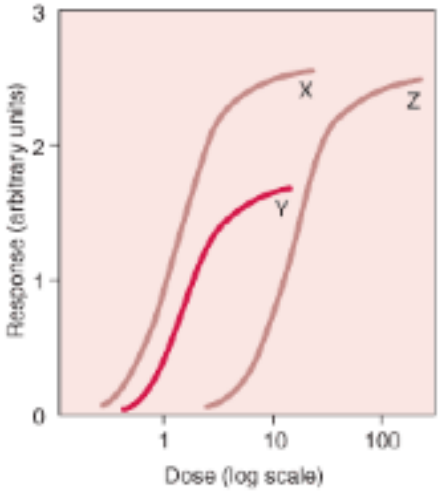


Figure 2.2. Comparison of dose response curve

Adverse drug response

An adverse drug reaction (ADR) is an injury caused by taking medication. ADRs may occur following a single dose or prolonged administration of a drug or result from the combination of two or more drugs. The meaning of this term differs from the term "side effect" because side effects can be beneficial as well as detrimental. The study of ADRs is the concern of the field known as pharmacovigilance. An adverse drug event (ADE) refers to any injury occurring at the time a drug is used, whether or not it is identified as a cause of the injury. An ADR is a special type of ADE in which a causative relationship can be shown. ADRs are only one type of medication-related harm, as harm can also be caused by omitting to take indicated medications.

ADRs may be classified by e.g. cause and severity. Cause

Type A: Augmented pharmacologic effects - dose dependent and predictable

Type A reactions, which constitute approximately 80% of adverse drug reactions, are usually a consequence of the drug's primary pharmacological effect (e.g. bleeding when using the anticoagulant warfarin) or a low therapeutic index of the drug (e.g. nausea from digoxin), and they are therefore predictable. They are dose-related and usually mild, although they may be serious or even fatal (e.g. intracranial bleeding from warfarin). Such reactions are usually due to inappropriate dosage, especially when drug elimination is impaired. The term 'side effects' is often applied to minor type A reactions.

Type B: Idiosyncratic

Types A and B were proposed in the 1970s, and the other types were proposed subsequently when the first two proved insufficient to classify ADRs.

Seriousness

The U.S Food and Drug Administration defines a serious adverse event as one when the patient outcome is one of the following:

- Death
- Life-threatening
- Hospitalization (initial or prolonged)
- Disability - significant, persistent, or permanent change, impairment, damage or disruption in the patient's body function/structure, physical activities or quality of life.

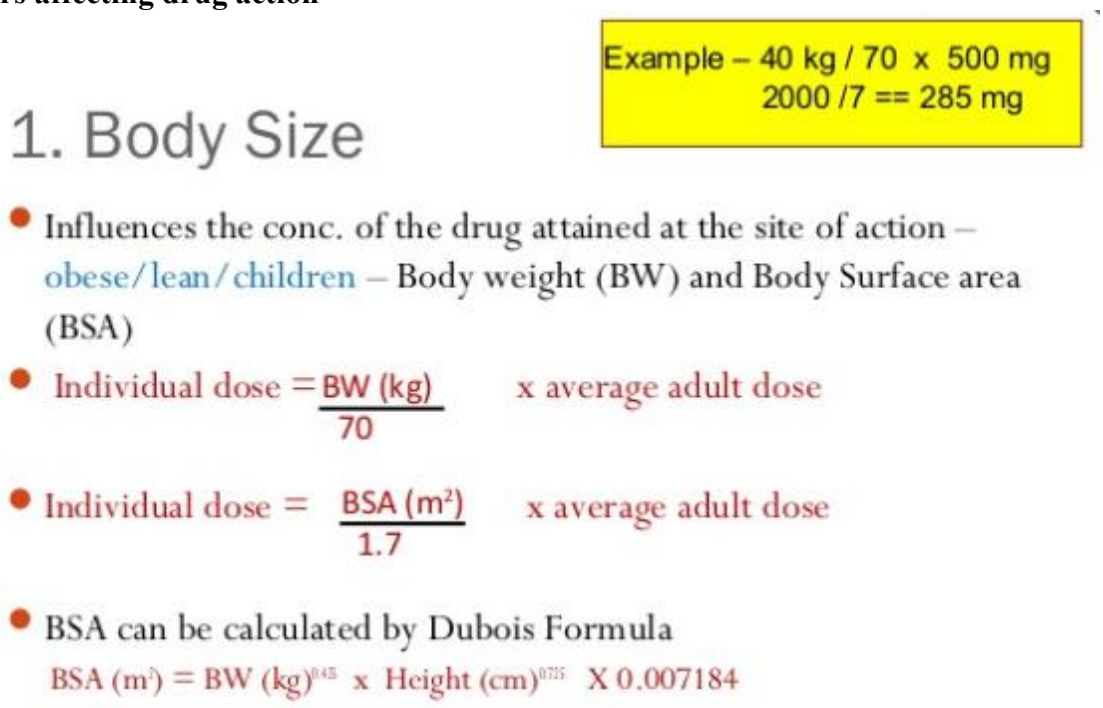
Congenital abnormality

- Requires intervention to prevent permanent impairment or damage

Severity is a point on an arbitrary scale of intensity of the adverse event in question. The terms "severe" and "serious" when applied to adverse events are technically very different. They are easily confused but can not be used interchangeably, requiring care in usage.

A headache is severe, if it causes intense pain. There are scales like "visual analog scale" that help clinicians assess the severity. On the other hand, a headache is not usually serious (but may be in case of subarachnoid haemorrhage, subdural bleed, even a migraine may temporally fit criteria), unless it also satisfies the criteria for seriousness listed above.

Factors affecting drug action



Example : (8 years / 8 years + 12) x 500 mg

- (8 x 500) / (8 + 12) = 200 mg

2. Age

- Young`s formula
- $\text{Child dose} = \frac{\text{Age}}{\text{Age} + 12} \times \text{adult dose}$
- Dilling`s formula
- $\text{Child dose} = \frac{\text{Age}}{20} \times \text{adult dose}$
- Note: Infants & children are not small adults – physiological differences
  - Low g.f.r and tubular transport – Gentamicin and Penicillin
  - Low hepatic drug metabolizing systems in newborns – *gray baby syndrome*
  - Blood brain barrier (BBB) is more permeable - Kernicterus
  - Absorption of drugs altered – lower gastric acidity ad slow intestinal transit
  - Faster transdermal absorption and faster rectal absorption - Diazepam
  - After 1 (one) year faster metabolism than adults – phenytoin, carbamazepine
  - **Caution** – Corticosteroids, androgens, tetracyclines …. **Elderly ????**

3. Sex

- Females have smaller body size – required doses are lower
- Digoxin in Maintenance therapy of heart failure – mortality higher
- Beta blockers, methyldopa, diuretics – sexual function interference in males
- Gynaecomastia – Metoclopramide, chlorpromazine, ketoconazole etc.
- Pregnancy – particularly 3rd trimester

4. Species and Race

- Species variation in drugs responses do exist
- Some strains of rabbits – resistant to atropine
- Rat and mice are resistant to digitalis
- Race – racial differences have been observed
- Blacks require higher doses of atropine and ephedrine, while Mongols require lower doses
- Africans – beta blockers are less effective
- SMON – Japan but not among Indians

5. Genetics

- Determinants of drug responses – transporter, enzymes, ion channels, receptors and couplers – controlled genetically – Individual variation of responses
- Pharmacogenetics: Use of genetic information to guide the choice of drug and dose on an individual basis – to identify individuals who are either more likely or less likely respond to a drug
  - so far genetic abnormalities have been identified
  - Personalized medicine goal yet to achieve
  - G-6PD deficiency – Primaquine, chlroquin, quinine, dapsone, aspirin
  - Malignant hypothermia with halothane etc.
  - Low variants of CYP2C9 – Warfarin bleeding; Isoniazid - acetylators

6. Route of administration

- Route determines the speed and intensity of drug response – Parenteral for speedy action
- A drug may have different actions via different routes – Magnesium sulfate

7. **Environmental factors**

- Drug metabolism may get induced – exposure to insecticides, carcinogens, tobacco smoke and charcoal broiled meat etc.
- Food interferes absorption of some drugs while enhances some drugs – ampicillin gets reduced griseofulvin gets enhanced
- Hypnotics taken at night

8. Psychological factors

- Efficacy of a drug can be affected by patient`s beliefs, attitudes and expectations – particularly CNS drugs – more GA in nervous and anxious patients – alcohol and performance
- **Placebo:** An *inert* substance which is given in the garb of medicine. Works by psychodynamic effects (not pharmacodynamics) – sometimes responses equivalent to active drugs
  - Placebo reactors
  - Induce psychological responses – release of endorphins in brain
  - Uses – Control device in clinical trials and to treat a patient
  - Lactose tablet/capsules or water injections etc.
- Nocebo: Negative psychodynamic effects of drugs

9. Pathological states

- Diseases can influence drug disposition – GIT diseases, Liver diseases, Kidney diseases, Congestive heart failure and Thyroid etc.
- **GIT:** Coeliac diseases – amoxicillin absorption decreased while Cephalexin and cotrimoxazole increased; Achlorohydria – Reduced aspirin absorption – NSAIDs aggravate peptic ulcer
- **Liver diseases:** Liver disease (cirrhosis) influence drug action
  - Increased bioavailability of drugs with high first pass metabolism
  - Serum albumin reduced – protein bound drugs like Warfarin – more free drug
  - Metabolism and elimination of drugs may be reduced – Doses should be reduced – Morphine, Propranolol, lignocaine etc.
  - Prodrugs are less effective (becampicillin)

- **Kidney diseases:** Pharmacokinetics of many drugs are affected
  - Clearance of drugs in unchanged form (aminoglycosides, digoxin, phenobarbitone) reduced – parallel to CL_{cr} - loading dose not altered – dose should be reduced
  - Plasma protein, albumin reduced – binding of acidic drugs affected
  - Permeability of BBB increased – Opiates etc. more CNS depression
  - Drugs acting via kidney mechanism – become ineffective – Thiazides and urinary antiseptics
- **CCF: (1)** Alter drug kinetics by decreased absorption (Thiazide), (2) modifying Volume of distribution Lignocaine), (3) retarding the elimination (lignocaine)- decreased perfusion and congestion of liver; reduced g.f.r, increased tubular reabsorption – doses need reduction

Thyroid diseases: Hypothyroid states – sensitive to digoxin, morphine and CNS depressants; Hyperthyroid states – resistant to inotropic action – prone to cause arrhythmia by digoxin

10. **Presence of other drugs:** Drug interactions – Pharmacokinetic and Pharmacodynamic
11. **Cumulation:** If Rate of administration > Rate of elimination – cumulataion. Slowly eliminating drugs are prone – Prolonged use of Chloroquine

12. Tolerance

- Requirement of higher dose of a drug to produce a given response – refractoriness – sulfonylureas in type 2 diabetes and beta-2 agonists in bronchial asthma - adaptive biological phenomena
  - Natural: Species/individual inherently less sensitive – Rabbits to atropine and Blacks to beta – blockers
  - Acquired: Repeated use of a drug in an individual who was initially responsive become non-responsive (tolerant) – CNS depressants
    - Due to uninterrupted presence of drug in the body – no tolerance to cocaine and atropine
    - Tolerance may develop to one action of the drug – but not to other action – Chlorpromazine, phenobarbitone, Morphine
  - Cross tolerance: Tolerance to pharmacologically related drugs – alcoholics to barbiturates and GA; Morphine and Pethidine

- Tolerance Mechanism:
  - Pharmacokinetic/drug disposition tolerance – effective concentration of the drug at the site of action is decreased – due to enhancement of elimination on chronic use – Barbiturates and Carbamazepine induce own metabolism
  - Pharmacodynamic tolerance: lesser drug action – cells of target organs become less responsive – Morphine, Barbiturates, Nitrates etc. …. Down regulation/desensitization of receptors
- Tachyphylaxis (Tachy – fast' phylaxis – protection): Rapid development of tolerance when a drug is repeated in quick succession – reduction of responses
  - Usually with indirectly acting drugs – Ephedrine, tyramine, nicotine etc. Also down regulation of receptors

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UNIT – III Drug action on Kidney and GIT– SMB203

III. Drug action on Kidney and GIT

Drugs acting on kidneys and GIT:

Chronic kidney disease, also called chronic kidney failure, describes the gradual loss of kidney function. Your kidneys filter wastes and excess fluids from your blood, which are then excreted in your urine. When chronic kidney disease reaches an advanced stage, dangerous levels of fluid, electrolytes and wastes can build up in your body. In the early stages of chronic kidney disease, you may have few signs or symptoms. Chronic kidney disease may not become apparent until your kidney function is significantly impaired. Treatment for chronic kidney disease focuses on slowing the progression of the kidney damage, usually by controlling the underlying cause. Chronic kidney disease can progress to end-stage kidney failure, which is fatal without artificial filtering (dialysis) or a kidney transplant. Signs and symptoms of chronic kidney disease develop over time if kidney damage progresses slowly. Signs and symptoms of kidney disease may include: Nausea, Vomiting, Loss of appetite, Fatigue and weakness, Sleep problems, Changes in how much you urinate, Decreased mental sharpness, Muscle twitches and cramps, Swelling of feet and ankles, Persistent itching, Chest pain, if fluid builds up around the lining of the heart, Shortness of breath, if fluid builds up in the lungs, High blood pressure (hypertension) that's difficult to control, Signs and symptoms of kidney disease are often nonspecific, meaning they can also be caused by other illnesses. Because your kidneys are highly adaptable and able to compensate for lost function, signs and symptoms may not appear until irreversible damage has occurred.

Chronic kidney disease occurs when a disease or condition impairs kidney function, causing kidney damage to worsen over several months or years. Diseases and conditions that cause chronic kidney disease include:

- Type 1 or type 2 diabetes
- High blood pressure
- Glomerulonephritis (gloe-mer-u-low-nuh-FRY-tis), an inflammation of the kidney's filtering units (glomeruli)
- Interstitial nephritis (in-tur-STISH-ul nuh-FRY-tis), an inflammation of the kidney's tubules and surrounding structures
- Polycystic kidney disease
- Prolonged obstruction of the urinary tract, from conditions such as enlarged prostate, kidney stones and some cancers
- Vesicoureteral (ves-ih-koe-yoo-REE-tur-ul) reflux, a condition that causes urine to back up into your kidneys
- Recurrent kidney infection, also called pyelonephritis (pie-uh-low-nuh-FRY-tis)

Diuretics - Classification of drugs,

Drugs that act on the kidney have important applications in renal, cardiovascular, and endocrine disorders. These disorders mainly involve sodium and water homeostasis. Each segment of the nephron—proximal convoluted tubule (PCT), thick ascending limb of the loop of Henle (TAL), distal convoluted tubule (DCT), and cortical collecting tubule (CCT)— has a different mechanism for reabsorbing sodium and other ions. The subgroups of the sodium-excreting diuretics are based on these sites and processes in the nephron. Several other drugs alter water excretion predominantly. The effects of the diuretic agents are predictable from knowledge of the function of the segment of the nephron in which they act.

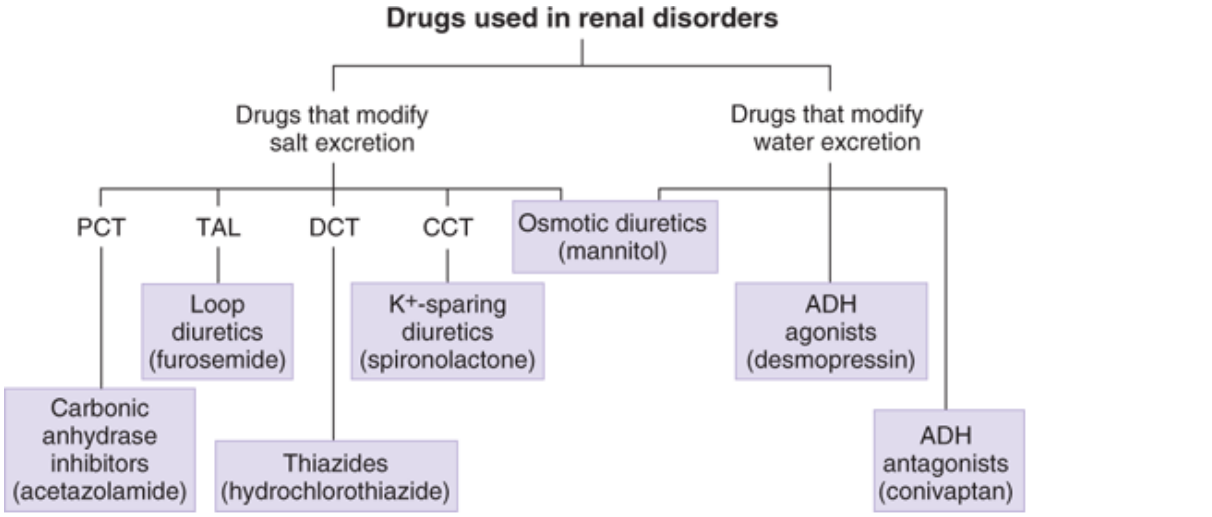

Figure 3.1. Drugs used in renal disorders

Renal transport mechanisms & diuretic drug groups

The kidney filters plasma water and solutes at the glomerulus at a very high rate (180 L/day) and must recover a significant percentage of most of these substances before excretion in the urine. The major transport mechanisms for the recovery of ions and water in the various segments of the nephron are shown. Because the mechanisms for reabsorption of salt and water differ in each of the 4 major tubular segments, the diuretics acting in these segments have differing mechanisms of action. Most diuretics act from the luminal side of the membrane. An exception is the aldosterone receptor antagonist group (spironolactone and eplerenone); these drugs enter the collecting tubule cell from the basolateral side and bind to the cytoplasmic aldosterone receptor. The kidney contains numerous adenosine and prostaglandin receptors. Agonists and antagonists at these receptors can alter renal function directly and alter the response to the diuretic agents. Prostaglandins are important in maintaining glomerular filtration. When synthesis of prostaglandins is inhibited, for example, by nonsteroidal anti-inflammatory drugs, the efficacy of most diuretics decreases.

Prototype drug- actions, and side effect

In pharmacology and pharmaceutics, a prototype drug is an individual drug that represents a drug class – group of medications having similar chemical structures, mechanism of action and mode of action. Prototypes are the most important, and typically the first developed drugs within the class, and are used as a reference to which all other drugs are compared. New medicines are designed to bind to receptors or enzymes and are tested in animal cells, tissues and whole organisms in a highly scientific process. Subsequently they are often administered to human subjects with tolerability as the primary objective. The process of development is considered to be linear and consecutive and passes through the famous four phases of development (Phase I– Phase IV). This is efficient for those projects for which the uncertainty about the development is low. There is, however, an increasing number of new prototypical compounds resulting from the increased biological knowledge with a high level of uncertainty. For these prototypical drugs development has to proceed in a much more adaptive manner, using tailor-made objectives, the development of special methodology and a cyclical rather than a linear type of project management.

An ethical committee should reject protocols for studies in humans for which the methodology does not allow the objectives to bereached. I studied the Phase I studies submitted to the competent authority for clinical trials in the Netherlands in 2009 (the

Central Committee on research Involving Human Subjects). For this assessment the full protocols and investigative medicinal product dossiers of these studies were examined. The system in the Netherlands guarantees completeness of the data set as submission in the national database is required by law. There were 26 Phase I studies in patients, of which 27% were first administrations of the drug to humans. most of these studies(65%) were in cancer and virtually all protocols involved highly innovative therapeutic concepts and products. Yet, 85% of all these studies had as their primary objectives the safety and tolerability of the compound and 50% attempted to reach a maximally tolerated dose as its end point. There were81 studies carried out in 4,754 healthy volunteers, of which 40% were first in human studies. All of these studies were performed using only safety and tolerability as the primary end points.

Tolerability can be determined in early drug development studies but it is questionable whether this is useful. The assumption is that the therapeutic dose of a medicine is more plausibly related to its pharmacological actions than to its toxic effects. The method of determining the therapeutic dose as a certain fraction of a toxic dose (the maximally tolerated dose)originates from a time when most drugs were relatively toxic (when these measures were probably closer together) and its value has been based on old literature28,29 relating to classical cytotoxic drugs. Therefore, this method only works for drugs with a narrow therapeutic margin for which the toxicity of the compound is linked to the clinically wanted effect. This is the case for the classical cytotoxic drugs because of bone marrow depression (the usual tolerability problem for these drugs) being a marker for an effect of the drug on rapidly dividing cells, but it is not applicable to any other modern medicines. Even the current generation of anticancer drugs is becoming increasingly selective.

Anti-diuretics

An antidiuretic is a substance that helps to control fluid balance in an animal's body by reducing urination, opposing diuresis. Its effects are opposite that of a diuretic. The major endogenous antidiuretics are antidiuretic hormone (ADH; also called vasopressin) and oxytocin. Both of those are also used exogenously as medications in people whose bodies need extra help with fluid balance via suppression of diuresis. In addition, there are various other antidiuretic drugs, some molecularly close to ADH or oxytocin and others not. Antidiuretics reduce urine volume, particularly in diabetes insipidus (DI), which is one of their main indications.

Classification of drugs, prototype drug- actions and side effect:

The three types of diuretic medications are called thiazide, loop, and potassium-sparing diuretics. All of them make your body excrete more fluids as urine.

Thiazide diuretics

Thiazides are the most commonly prescribed diuretics. They’re most often used to treat high blood pressure. These drugs not only decrease fluids, they also cause your blood vessels to relax. Thiazides are sometimes taken with other medications used to lower blood pressure. Examples of thiazides include: chlorthalidone, hydrochlorothiazide (Microzide), metolazone, indapamide,

Loop diuretics

Loop diuretics are often used to treat heart failure. Examples of these drugs include: torsemide (Demadex), furosemide (Lasix), bumetanide

Potassium-sparing diuretics

Potassium-sparing diuretics reduce fluid levels in your body without causing you to lose potassium, an important nutrient. The other types of diuretics cause you to lose potassium, which can lead to health problems such as arrhythmia. Potassium-sparing diuretics may be prescribed for people at risk of low potassium levels, such as those who take

other medications that deplete potassium. Potassium-sparing diuretics don't reduce blood pressure as well as the other types of diuretics do. Therefore, your doctor may prescribe a potassium- sparing diuretic with another medication that also lowers blood pressure.
Examples of potassium-sparing diuretics include: amiloride, triamterene (Dyrenium), spironolactone (Aldactone), eplerenone (Inspra)

Drugs for peptic ulcer - classification of drugs

Peptic ulcers can be broadly classified into gastric ulcers and duodenal ulcers. Normally the stomach wall is protected by the mucosa against irritation of gastric acid. When the mucosa is damaged or when the stomach produces so much gastric acid that the protective lining is eroded with subsequent inflammation or necrosis, a local ulcer will develop. The commonest symptom of peptic ulcers is intermittent abdominal pains, especially in the middle of the night or when you are hungry. Other symptoms include bloating, nausea, burping and loss of appetite. In severe cases, it may result in gastrorrhagia, an illness characterized by black stool or vomitus resembling ground coffee.

Causes of Ulcers

- Congenital hyperacidity.
- Mental strain and emotional stress that make the nervous system stimulate the excessive production of gastric acid.
- Undesirable eating habits, irregular meals or overeating.
- Smoking and excessive alcohol are direct causes of increased morbidity.
- Drugs such as aspirin and painkillers for rheumatism irritate and damage gastric mucosa.

Classification of the Drugs

Drugs for peptic ulcers are mainly classified into three categories:

Antacids:

They neutralise gastric acid, thereby relieving or eliminating the irritation and erosion to the stomach wall and the ulcer sites. Common examples include magnesium trisilicate and aluminium hydroxide. They are available in the form of chewable pills and liquids.

Anticholinergics:

They suppress the secretion of gastric acid, reduce gastroinstestinal movement and relieve stomach cramps. Common examples include propantheline bromide and scopolamine methylbromide.

H2 receptor antagonists:

They are commonly known as specific drugs. They directly suppress the secretion of gastric acid. Common examples include cimetidine and ranitidine.

Side Effects of the Drugs

Antacids suppress the absorption of other anti-ulcer drugs, tetracyclines, iron pills, etc and affect their efficacy. These two types of drugs should therefore be taken separately, with an interval of one or two hours. Antacids of different formulas may produce mild laxative effect or result in constipation.

Side effects of anticholinergics include glaucoma, urinary retention, rapid heartbeat and mouth dryness.

H2 receptor antagonists have fewer side effects and the major ones are the loss of directional sense and allergic reactions. Such side effects will subside if medication stops.

prototype drug actions and side effect

Prototype Medications can include: Antibiotic medications to kill H. pylori. If H. pylori is found in your digestive tract, your doctor may recommend a combination of antibiotics to kill the bacterium. These may include amoxicillin (Amoxil), clarithromycin

(Biaxin), metronidazole (Flagyl), tinidazole (Tindamax), tetracycline (Tetracycline HCL) and levofloxacin (Levaquin).

The antibiotics used will be determined by where you live and current antibiotic resistance rates. You'll likely need to take antibiotics for two weeks, as well as additional medications to reduce stomach acid, including a proton pump inhibitor and possibly bismuth subsalicylate (Pepto-Bismol). Medications that block acid production and promote healing. Proton pump inhibitors — also called PPIs — reduce stomach acid by blocking the action of the parts of cells that produce acid. These drugs include the prescription and over-the-counter medications omeprazole (Prilosec), lansoprazole (Prevacid), rabeprazole (Aciphex), esomeprazole (Nexium) and pantoprazole (Protonix).

Long-term use of proton pump inhibitors, particularly at high doses, may increase your risk of hip, wrist and spine fracture. Ask your doctor whether a calcium supplement may reduce this risk.

Medications to reduce acid production. Acid blockers — also called histamine (H-2) blockers

reduce the amount of stomach acid released into your digestive tract, which relieves ulcer pain and encourages healing.

Available by prescription or over-the-counter, acid blockers include the medications ranitidine, famotidine (Pepcid), cimetidine (Tagamet HB) and nizatidine (Axid AR).

Antacids that neutralize stomach acid. Your doctor may include an antacid in your drug regimen. Antacids neutralize existing stomach acid and can provide rapid pain relief. Side effects can include constipation or diarrhea, depending on the main ingredients.
Antacids can provide symptom relief, but generally aren't used to heal your ulcer.

Medications that protect the lining of your stomach and small intestine. In some cases, your doctor may prescribe medications called cytoprotective agents that help protect the tissues that line your stomach and small intestine.

Options include the prescription medications sucralfate (Carafate) and misoprostol (Cytotec).

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UNIT – IV Cardiovascular Physiology– SMB203

IV. Cardiovascular Pharmacology:

Cardiovascular Pharmacology

Hypertension - classification of drugs, prototype drug- actions and side effect.

Many therapeutic agents can be used for the pharmacologic management of hypertension. The general recommendation established by the Seventh Report of the Prevention, Detection, Evaluation, and Treatment of the Joint National Committee on High Blood Pressure is to initiate a thiazide-type diuretic initially for stage 1 hypertensive patients without compelling indications for other therapies. Drugs such as angiotensin converting enzyme inhibitors(ACEIs), calcium channel blockers (CCBs), angiotensin- receptor blockers (ARBs), beta-blockers, and diuretics are all considered acceptable alternative therapies in patients with hypertension. The available antihypertensive agents are generally equally effective in lowering blood pressure however; there may be interpatient variability that can affect the way a patient will respond to one treatment over another. There are a number of types and classes of drugs available for the management and treatment of high blood pressure (hypertension). Your doctor or other health care professional will prescribe a drug that fits your specific needs based on your medical condition, and any other existing health problems you may have, for example, kidney disease, heart disease, or diabetes. Your doctor also may recommend other therapies and lifestyle changes like getting more exercise, managing stress, and eating a healthy diet.

Angiotensin converting enzyme (ACE) inhibitors

Angiotensin converting enzyme (ACE) inhibitors are blood pressure medications that inhibit the activity of the enzyme angiotensin converting enzyme (ACE), which is important for controlling blood pressure.

Angiotensin II is a very potent chemical formed in the blood by ACE from, angiotensin I. When formed, angiotensin II causes the muscles surrounding blood vessels to contract, thus narrowing the vessels and increasing blood pressure. ACE inhibitors are medications that inhibit the activity of ACE which decreases the production of angiotensin II. As a result, these medications cause the blood vessels to enlarge or dilate, and this reduces blood pressure. This lower blood pressure makes it easier for the heart to pump blood and can improve the function of a failing heart. In addition, the progression of kidney disease due to high blood pressure or diabetes is slowed.

Common side effects of this ACE inhibitors

- Cough
- Low blood pressure (hypotension)
- Fatigue
- Headache
- Increased blood potassium levels

This list is not does not include all side effects or adverse events for ACE inhibitors. This class of medicine also are used for other health conditions, for example:

- Prevention and treatment of diabetes and kidney disease Heart failure
- Examples of generic and brand names available for ACE inhibitors
- enalapril (Vasotec)
- captopril (Capoten)
- lisinopril (Zestril and Prinivil)
- benazepril (Lotensin)
- quinapril (Accupril)
- perindopril (Aceon)
- ramipril (Altace)
- trandolapril (Mavik)

- fosinopril (Monopril)
- moexipril (Univasc) Angiotensin receptor blockers (ARBs)

Angiotensin II receptor blockers (ARBs) are medications used to treat elevated blood pressure, or hypertension. These medications that block the action of angiotensin II by preventing angiotensin II from binding to angiotensin II receptors on the muscles surrounding blood vessels. As a result, blood vessels enlarge (dilate), and blood pressure is reduced. Reduced blood pressure makes it easier for the heart to pump blood and can improve heart failure. In addition, the progression of kidney disease due to high blood pressure or diabetes is slowed. ARBs have effects similar to ACE inhibitors, but ACE inhibitors act by preventing the formation of angiotensin II rather than by blocking the binding of angiotensin II to muscles on blood vessels.

CHF - classification of drugs, prototype drug- actions and side effect,

Coronary Artery Disease- classification of drugs, prototype drug- actions and side effect, Arrhythmia - classification of drugs, prototype drug- actions and side effect. This list is not does not include all side effects or adverse events for ARBs. This class of medicine also are used for other health conditions, for example:

- Prevention and treatment of diabetes kidney disease
- Heart failure
- Examples of generic and brand names available for ARBs
- losartan (Cozaar)
- irbesartan (Avapro)
- valsartan (Diovan)
- candesartan (Atacand)
- olmesartan (Benicar)
- telmisartan (Micardis)
- eprosartan (Teveten)
- azilsartan (Edarbi)
- Beta-blockers

Beta blockers are medications that block norepinephrine and epinephrine (adrenaline) from binding to both beta 1 and beta 2 receptors on organs and muscles, including the muscles surrounding blood vessels that cause the blood vessels to narrow and the heart to beat. By blocking the effect of norepinephrine and epinephrine, beta blockers reduce blood pressure by dilating blood vessels and reducing heart rate. They also may constrict air passages because stimulation of beta receptors in the lung cause the muscles that surround the air passages to contract.

Common side effects of beta blockers

- Fatigue
- Dizziness
- Shortness of breath
- Impotence
- Low blood pressure

This list is not does not include all side effects or adverse events for beta blockers. This class of medicine also are used for other health conditions, for example:

- Heart failure
- Chest pain (angina)
- Hyperthyroidism
- Fast heart rate
- Migraine
- Examples of brand and generic names available for beta blockers

- acebutolol (Sectral)
- atenolol (Tenormin)
- betaxolol (Kerlone has been discontinued)
- bisoprolol fumarate (Zebeta)
- carteolol (Cartrol, discontinued)
- carvedilol (Coreg)
- esmolol (Brevibloc)
- labetalol (Trandate [Normodyne - discontinued])
- metoprolol (Lopressor, Toprol XL)
- nadolol (Corgard)
- nebivolol (Bystolic)
- penbutolol (Levatol has been discontinued)
- pindolol (Visken, discontinued)
- propranolol (Hemangeol, Inderal LA Inderal XL, InnoPran XL)
- timolol (Blocadren, discontinued)

Calcium channel blockers (CCBs)

Calcium is needed by all muscle cells, including those of the heart and muscles and surrounding arteries, in order for the cells to contract. CCBs inhibit the movement of calcium into muscle cells. The reduction in calcium reduces the force of the heart's muscular pumping action (cardiac contraction) and thereby reduces blood pressure. These medications also relax the muscle cells surrounding the arteries to further reduce blood pressure. Three major types of calcium channel blockers are available. One type is the dihydropyridines, which do not slow the heart rate or cause other abnormal heart rates or rhythms (cardiac arrhythmias). They are commonly used for treating high blood pressure and are very effective in reducing blood pressure in African Americans.

Common side effects of CCBs

- Water retention in the arm and legs (peripheral edema)
- Constipation
- Shortness of breath
- Rash
- Headache

This list is not does not include all side effects or adverse events for CCBs. This class of medicine also are used for other health conditions, for example:

- Migraine headache prevention
- Chest pain (angina)
- Abnormal heart beats
- Essential tremor
- Pheochromocytoma
- Hypertrophic subaortic stenosis
- Portal hypertension
- Examples of brand and generic names available for CCBs
- amlodipine (Norvasc)
- amlodipine and atorvastatin (Caduet)
- amlodipine and benazepril (Lotrel)
- amlodipine and valsartan (Exforge)
- amlodipine and telmisartan (Twynsta)
- amlodipine and olmesartan (Azor)
- amlodipine and olmesartan and hydrochlorothiazide (Tribenzor)
- amlodipine and aliskiren (Tekamlo has been discontinued in the US)

- amlodipine and aliskiren and hydrochlorothiazide (Amturnide has been discontinued in the US)
- amlodipine and perindopril (Prestalia)
- clevidipine (Cleviprex)
- diltiazem (Cardizem)
- felodipine (Plendil has been discontinued in the US)
- isradipine (Dynacirc has been discontinued in the US)
- nifedipine (Procardia, Procardia XL, Adalat CC, Afeditab)
- nicardipine (Cardene, Cardene SR)
- nimodipine (Nimotop has been discontinued in the US)
- nisoldipine (Sular)
- verapamil (Calan)

The other two types of CCBs are referred to as the non-dihydropyridine agents. One type is verapamil (Calan, Covera, Isoptin, Verelan) and the other is diltiazem (Cardizem, Tiazac, Dilacor, and Diltia).

Diuretics

Diuretics are among the oldest known medications for treating high blood pressure. They work in the tiny tubes (tubules) of the kidneys to promote the removal of salt from the body. Water (fluid) also is removed along with the salt; however, the exact mechanism whereby diuretics lower blood pressure is not clearly known. The leading theory is that they directly cause the muscles surrounding blood vessels to relax. Diuretics may be used alone for high blood pressure. More frequently, however, low doses of diuretics are used in combination with other medications for high blood pressure to enhance the effect of the other medications.

Common side effects of diruetics

- Dehydration
- Low blood potassium
- Low blood pressure
- Fatigue
- Increased blood glucose
- Increased level of uric acid

This list is not does not include all side effects or adverse events for diuretics. This class of medicine also are used for other health conditions, for example:

- Congestive heart failure
- Peripheral edema
- Pulmonary edema
- High potassium blood levels
- Most commonly used diuretics to treat hypertension
- hydrochlorothiazide (Hydrodiuril)
- chlorthalidone
- The loop diuretics furosemide (Lasix), bumetanide (Bumex), and torsemide (Demadex)
- The combination of triamterene and hydrochlorothiazide (Dyazide)
- metolazone (Zaroxolyn)

The thiazide drugs are related to sulfa drugs. For those individuals who are allergic to sulfa drugs, ethacrynic acid, a loop diuretic, is a good option. Diuretics probably should not be used in pregnant women

Alpha-blockers

Muscles surrounding blood vessels have alpha receptors. Stimulation of alpha receptors, like stimulation of beta receptors, cause the muscles surrounding the arteries to contract and narrow the arteries. By blocking the alpha receptor, alpha-blockers relax the muscles and lower blood pressure.

Common side effects of alpha blockers

- Low blood pressure
- Dizziness
- Nausea
- Weakness

Examples of generic and brand names available for alpha blockers

- terazosin (Hytrin - brand name discontinued in the US)
- doxazosin (Cardura)

This list is not does not include all side effects or adverse events for alpha blockers. Alpha blockers also are used for treating a health problem called benign prostate hyperplasia (BPH).

Alpha-beta blockers

Alpha-beta blockers work the same way as alpha-blockers but also slow the heartbeat as beta- blockers do. As a result, less blood is pumped through the vessels, vessels dilate and blood pressure is lowered.

Common side effects of alpha blockers

- Dizziness
- Fatigue
- Slow heart rate
- Shortness of breath
- Weight gain
- Low blood pressure

This list is not does not include all side effects or adverse events for these medications. This class of medicine also are used for other health conditions, for example:

- Heart failure
- Heart attack prevention
- Examples of brand and generic names available for alpha blockers
- carvedilol (Coreg), and
- labetalol (Trandate). Normodyne is discontinued brand in the US.
- Clonidine

Clonidine (Catapres, Catpres-TTS) is an inhibitor of the nervous system in the brain. These inhibitors of the nervous system act by binding to receptors on nerves in the brain to reduce the transmission of messages from the nerves in the brain to nerves in other areas of the body. By inhibiting transmission to nerves outside of the brain that innervate muscle cells of the heart and blood vessels, heart rate and blood pressure are reduced.

Common side effects

- Low blood pressure
- Drowsiness
- Headache
- Withdrawal symptoms

This list is not does not include all side effects or adverse events for Clonidine. This class of medicine also are used for other health conditions, for example:

- Cancer pain
- Restless syndrome
- Tourette's syndrome

- Opioid withdrawal
- Postherpetic neuralgia
- Smoking cessation Aliskiren (Tekturna)

The kidneys produce renin when they detect low blood pressure. Renin stimulates the production of angiotensin I, a protein which is converted to angiotensin II by angiotensin-converting enzyme (ACE) in the lungs. Angiotensin II is a powerful constrictor of blood vessels, and constricting blood vessels increases blood pressure. Angiotensin II also causes the secretion of an additional blood pressure elevating hormone in the adrenal glands called aldosterone, which helps the body retain sodium. Aliskiren blocks the effects of renin and angiotensin so that blood pressure does not increase.

Common side effects

- Diarrhea
- Increased blood levels of potassium
- Abnormal kidney function test results

Minoxidil

Minoxidil is a vasodilator. Vasodilators are muscle relaxants that work directly on the muscles surrounding the arteries throughout the body. The arteries then dilate and blood pressure is reduced.

Common side effects

- Edema
- Increased heart rate
- Weight gain
- Headache

This list is not does not include all side effects or adverse events for Minoxidil. Other uses Male baldness (topical foam and solution). High blood pressure (hypertension) medications include drugs from a variety of different drug classes and types. ACE inhibitors, ARB (angiotensin receptor blockers), beta blockers, calcium channel blockers (CCBs), diuretics, alpha-blockers, alpha-beta blockers. Clonidine (Catapres) and minoxidil also are drugs prescribed for the treatment of high blood pressure. Side effects, warnings and precautions, safety information, and pregnancy and breastfeeding safety information should be reviewed prior to taking any medication. CHF - classification of drugs, prototype drug-actions and side effect Congestive heart failure medications overview Congestive heart failure is a chronic (ongoing) condition. Discuss all medications, herbs, supplements you are taking with your doctor. Listed are some of the medications used to treat congestive heart failure.

ACE inhibitors (angiotensin converting enzyme)

ACE inhibitors have been used for the treatment of hypertension for more than 20 years. This class of drugs has also been extensively studied in the treatment of congestive heart failure. These medications block the formation of angiotensin II, a hormone with many potentially adverse effects on the heart and circulation in patients with heart failure. In multiple studies of thousands of patients, these drugs have demonstrated a remarkable improvement of symptoms in patients, prevention of clinical deterioration, and prolongation of survival. In addition, they have been recently been shown to prevent the development of heart failure and heart attacks. The wealth of the evidence supporting the use of these agents in heart failure is so strong that ACE inhibitors should be considered in all patients with heart failure, especially those with heart muscle weakness.

Possible side effects of these drugs include:

- a nagging, dry cough,
- low blood pressure,

- worsening kidney function and electrolyte imbalances, and
- rarely, true allergic reactions.

When used carefully with proper monitoring, however, the majority of individuals with congestive heart failure tolerate these medications without significant problems. Examples of ACE inhibitors include:

- captopril (Capoten),
- enalapril (Vasotec),
- lisinopril (Zestril, Prinivil),
- benazepril (Lotensin), and
- ramipril (Altace).

For those individuals who are unable to tolerate the ACE inhibitors, an alternative group of drugs, called the angiotensin receptor blockers (ARBs), may be used. These drugs act on the same hormonal pathway as the ACE inhibitors, but instead block the action of angiotensin II at its receptor site directly. A small, early study of one of these agents suggested a greater survival benefit in elderly congestive heart failure patients as compared to an ACE inhibitor. However, a larger, follow-up study failed to demonstrate the superiority of the ARBs over the ACE inhibitors. Further studies are underway to explore the use of these agents in congestive heart failure both alone and in combination with the ACE inhibitors.

Possible side effects of these drugs are similar to those associated with the ACE inhibitors, although the dry cough is much less common. Examples of this class of medications include:

- losartan (Cozaar),
- candesartan (Atacand),
- telmisartan (Micardis),
- valsartan (Diovan),
- irbesartan (Avapro), and
- olmesartan (Benicar).

Beta-blockers

Certain hormones, such as epinephrine (adrenaline), norepinephrine, and other similar hormones, act on the beta receptor's of various body tissues and produce a stimulative effect. The effect of these hormones on the beta receptors of the heart is a more forceful contraction of the heart muscle. Beta-blockers are agents that block the action of these stimulating hormones on the beta receptors of the body's tissues. Since it was assumed that blocking the beta receptors further depressed the function of the heart, beta-blockers have traditionally not been used in persons with congestive heart failure. In congestive heart failure, however, the stimulating effect of these hormones, while initially useful in maintaining heart function, appears to have detrimental effects on the heart muscle over time.

However, studies have demonstrated an impressive clinical benefit of beta-blockers in improving heart function and survival in individuals with congestive heart failure who are already taking ACE inhibitors. It appears that the key to success in using beta-blockers in congestive heart failure is to start with a low dose and increase the dose very slowly. At first, patients may even feel a little worse and other medications may need to be adjusted.

Possible side effects include:

- fluid retention,
- low blood pressure,
- low pulse, and
- general fatigue and lightheadedness.

Beta-blockers should generally not be used in people with certain significant diseases of the airways (for example, asthma, emphysema) or very low resting heart rates. While carvedilol (Coreg) has been the most thoroughly studied drug in the setting of congestive heart failure, studies of other beta-blockers have also been promising. Research comparing carvedilol directly with other beta-blockers in the treatment of congestive heart failure is ongoing. Long acting metoprolol (Toprol XL) is also very effective in individuals with congestive heart failure.

Digoxin (Lanoxin)

Digoxin (Lanoxin) has been used in the treatment of congestive heart failure for hundreds of years. It is naturally produced by the foxglove flowering plant. Digoxin stimulates the heart muscle to contract more forcefully. It also has other actions, which are not completely understood, that improve congestive heart failure symptoms and can prevent further heart failure. However, a large-scale randomized study failed to demonstrate any effect of digoxin on mortality.

Digoxin is useful for many patients with significant congestive heart failure symptoms, even though long-term survival may not be affected. Potential side effects include:

- nausea,
- vomiting,
- heart rhythm disturbances,
- kidney dysfunction, and
- electrolyte abnormalities.

These side effects, however, are generally a result of toxic levels in the blood and can be monitored by blood tests. The dose of digoxin may also need to be adjusted in patients with significant kidney impairment.

Diuretics

Diuretics are often an important component of the treatment of congestive heart failure to prevent or alleviate the symptoms of fluid retention. These drugs help keep fluid from building up in the lungs and other tissues by promoting the flow of fluid through the kidneys. Although they are effective in relieving symptoms such as shortness of breath and leg swelling, they have not been demonstrated to positively impact long-term survival.

Nevertheless, diuretics remain key in preventing deterioration of the patient's condition thereby requiring hospitalization. When hospitalization is required, diuretics are often administered intravenously because the ability to absorb oral diuretics may be impaired, when congestive heart failure is severe. Potential side effects of diuretics include:

- dehydration,
- electrolyte abnormalities,
- particularly low potassium levels,
- hearing disturbances, and
- low blood pressure.

It is important to prevent low potassium levels by taking supplements, when appropriate. Such electrolyte disturbances may make patients susceptible to serious heart rhythm disturbances. Examples of various classes of diuretics include:

- furosemide (Lasix),
- hydrochlorothiazide (Hydrodiuril),
- bumetanide (Bumex),
- torsemide (Demadex),
- spironolactone (Aldactone), and
- metolazone (Zaroxolyn).

One particular diuretic has been demonstrated to have surprisingly favorable effects on survival in congestive heart failure patients with relatively advanced symptoms. Spironolactone (Aldactone) has been used for many years as a relatively weak diuretic in the treatment of various diseases. Among other things, this drug blocks the action of the hormone aldosterone.

Aldosterone has many theoretical detrimental effects on the heart and circulation in congestive heart failure. Its release is stimulated in part by angiotensin II (see ACE inhibitors, previously). In patients taking ACE inhibitors, however, there is an "escape" phenomenon in which aldosterone levels can increase despite low levels of angiotensin II. Medical researchers have found that spironolactone (Aldactone) can improve the survival rate of patients with congestive heart failure. In that the doses used in the study were relatively small, it has been theorized that the benefit of the drug was in its ability to block the effects of aldosterone rather than its relatively weak action as a diuretic (water pill). Possible side effects of this drug include elevated potassium levels and, in males, breast tissue growth (gynecomastia). Another aldosterone inhibitor is eplerenone (Inspra).

Coronary Artery Disease- classification of drugs,

The heart muscle needs a constant supply of oxygen-rich blood. The coronary arteries, which branch off the aorta just after it leaves the heart, deliver this blood. Coronary artery disease that narrows one or more of these arteries can block blood flow, causing chest pain (angina) or an acute coronary syndrome (see also Overview of Coronary Artery Disease).

In an acute coronary syndrome, sudden blockage in a coronary artery greatly reduces or cuts off the blood supply to an area of the heart muscle (myocardium). The lack of blood supply to any tissue is termed ischemia. If the supply is greatly reduced or cut off for more than a few minutes, heart tissue dies. A heart attack, also termed myocardial infarction (MI), is death of heart tissue due to ischemia. There are many different reasons doctors give drugs to people with coronary artery disease:

- To relieve chest pain by reducing the heart's workload and widening arteries (nitrates)
- To prevent angina and acute coronary symptoms from occurring (beta-blockers, calcium channel blockers, and sometimes ranolazine)
- To prevent and reverse coronary artery narrowing from atherosclerosis (angiotensin-converting enzyme [ACE] inhibitors, angiotensin II receptor blockers [ARBs], statins, and antiplatelet drugs)
- To open a blocked artery (clot-dissolving drugs, anticoagulants)

Nitrates

Most people are given nitroglycerin, which relieves pain by reducing the workload of the heart and possibly by dilating arteries. Usually, it is first given under the tongue, then intravenously.

Morphine

Most people who have had a heart attack are experiencing severe discomfort and anxiety. Morphine has a calming effect and reduces the workload of the heart. It is given when nitroglycerin cannot be used or is not effective; however, recent data suggest it may interact with antiplatelet drugs and reduce their effectiveness.

Beta-blockers

Because decreasing the heart’s workload also helps limit tissue damage, a beta-blocker is usually given to slow the heart rate. Slowing the rate enables the heart to work less hard and reduces the area of damaged tissue.

Calcium channel blockers

Calcium channel blockers prevent blood vessels from narrowing (constricting) and can counter coronary artery spasm. All calcium channel blockers reduce blood pressure.

Some of these drugs, such as verapamil and diltiazem, may also reduce the heart rate. This effect can be useful to many people, especially those who cannot take beta-blockers or who do not get enough relief from nitrates.

Ranolazine

Ranolazine is a drug used to treat angina in people who continue to have symptoms despite taking all other antianginal therapy. It may be more effective in women than in men.

Angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers

Angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) can reduce heart enlargement and increase the chance of survival for many people. Therefore, these drugs are usually given in the first few days after a heart attack and prescribed indefinitely.

Statins

Statins have long been used to help prevent coronary artery disease, but doctors have recently found that they also have short-term benefit for people with an acute coronary syndrome. Doctors give a statin to people who are not already taking one.

Antiplatelet drugs

People who think they may be having a heart attack should chew an aspirin tablet immediately after calling an ambulance. If aspirin is not taken at home or given by emergency personnel, it is immediately given at the hospital. This therapy improves the chances of survival by reducing the size of the clot (if present) in the coronary artery. People may also be given other types of antiplatelet drugs such as clopidogrel, ticlopidine, or ticagrelor taken by mouth, or glycoprotein IIb/IIIa inhibitors given by vein (intravenously).

Clot-dissolving drugs

Clot-dissolving drugs (thrombolytic drugs) are given intravenously to open the arteries if percutaneous coronary interventions cannot be done within 90 minutes after the person arrives at the hospital.

Anticoagulants

Most people are also given an anticoagulant drug, such as heparin, to help prevent the formation of additional blood clots.

Often, oxygen is given through nasal prongs or a face mask. Providing more oxygen to the heart helps keep heart tissue damage to a minimum.

Arrhythmia - classification of drugs, prototype drug- actions and side effect.

The need for treatment of arrhythmias depends on the symptoms and the seriousness of the arrhythmia. Treatment is directed at causes. If necessary, direct antiarrhythmic therapy, including antiarrhythmic drugs, cardioversion-defibrillation, implantable cardioverter- defibrillators (ICDs), pacemakers (and a special form of pacing, cardiac resynchronization therapy), catheter ablation, surgery, or a combination, is used. Most antiarrhythmic drugs are grouped into 4 main classes (Vaughan Williams classification) based on their dominant cellular electrophysiologic effect (see table Antiarrhythmic Drugs (Vaughan Williams Classification)).

- → Class I: Class I drugs are subdivided into subclasses a, b, and c. Class I drugs are sodium channel blockers (membrane-stabilizing drugs) that block fast sodium channels, slowing conduction in fast-channel tissues (working atrial and ventricular myocytes, His-Purkinje system).
- → Class II: Class II drugs are beta-blockers, which affect predominantly slow-channel tissues (sinoatrial [SA] and atrioventricular [AV] nodes), where they decrease rate of automaticity, slow conduction velocity, and prolong refractoriness.
- → Class III: Class III drugs are primarily potassium channel blockers, which prolong action potential duration and refractoriness in slow- and fast-channel tissues.

→ Class IV: Class IV drugs are the non-dihydropyridine calcium channel blockers, which depress calcium-dependent action potentials in slow-channel tissues and thus decrease the rate of automaticity, slow conduction velocity, and prolong refractoriness.

Digoxin and adenosine are not included in the Vaughan Williams classification. Digoxin shortens atrial and ventricular refractory periods and is vagotonic, thereby prolonging AV nodal conduction and AV nodal refractory periods. Adenosine slows or blocks AV nodal conduction and can terminate tachyarrhythmias that rely upon AV nodal conduction for their perpetuation. Class I Antiarrhythmic Drugs

- Class I antiarrhythmic drugs are Sodium channel blockers (membrane-stabilizing drugs), which block fast sodium channels, slowing conduction in fast-channel tissues (working atrial and ventricular myocytes, His-Purkinje system)
- In the electrocardiogram (ECG), this effect may be reflected as widening of the P wave, widening of the QRS complex, prolongation of the PR interval, or a combination.
- Class I drugs are subdivided based on the kinetics of the sodium channel effects:
- Class Ib drugs have fast kinetics. Class Ic drugs have slow kinetics.
- Class Ia drugs have intermediate kinetics.

The kinetics of sodium channel blockade determine the heart rates at which their electrophysiologic effects become manifest. Because class Ib drugs have fast kinetics, they express their electrophysiologic effects only at fast heart rates. Thus, an ECG obtained during normal rhythm at normal rates usually shows no evidence of fast-channel tissue conduction slowing. Class Ib drugs are not very potent antiarrhythmics and have minimal effects on atrial tissue.

Class Ic drugs have slow kinetics, so they express their electrophysiologic effects at all heart rates. Thus, an ECG obtained during normal rhythm at normal heart rates usually shows fast-channel tissue conduction slowing. Class Ic drugs are more potent antiarrhythmics.

Class Ia drugs have intermediate kinetics, so their fast-channel tissue conduction slowing effects may or may not be evident on an ECG obtained during normal rhythm at normal rates. Class Ia drugs also block repolarizing potassium channels, prolonging the refractory periods of fast-channel tissues. On the ECG, this effect is reflected as QT-interval prolongation even at normal rates. Class Ib drugs and class Ic drugs do not block potassium channels directly.

The primary indications are supraventricular tachycardia (SVT) for class Ia and Ic drugs and ventricular tachycardia (VTs) for all class I drugs. Adverse effects of class I drugs include proarrhythmia, a drug-related arrhythmia worse than the arrhythmia being treated, which is the most worrisome adverse effect. All class I drugs may worsen VTs. Class I drugs also tend to depress ventricular contractility. Because these adverse effects are more likely to occur in patients with a structural heart disorder, class I drugs are not generally recommended for such patients. Thus, these drugs are usually used only in patients who do not have a structural heart disorder or in patients who have a structural heart disorder but who have no other therapeutic alternatives. There are other adverse effects of class I drugs that are specific to the subclass or individual drug.

Class Ia antiarrhythmic drugs

Class Ia drugs have kinetics that are intermediate between the fast kinetics of class Ib and the slow kinetics of class Ic. Their fast-channel tissue conduction slowing effects may or may not be evident on an ECG obtained during normal rhythm at normal rates. Class Ia drugs block repolarizing potassium channels, prolonging the refractory periods of fast-

channel tissues. On the ECG, this effect is reflected as QT-interval prolongation even at normal rates.

Class Ia drugs are used for suppression of atrial premature beats, ventricular premature beats, supraventricular tachycardia, ventricular tachycardia, atrial fibrillation, atrial flutter, and ventricular fibrillation. The primary indications are supraventricular and ventricular tachycardias.

Class Ia drugs may cause torsades de pointes ventricular tachycardia. Class Ia drugs may organize and slow atrial tachyarrhythmias enough to permit 1:1 AV conduction with marked acceleration of the ventricular response rate.

Class Ib antiarrhythmic drugs

Class Ib drugs have fast kinetics; they express their electrophysiologic effects only at fast heart rates. Thus, an ECG obtained during normal rhythm at normal rates usually shows no evidence of fast-channel tissue conduction slowing. Class Ib drugs are not very potent antiarrhythmics and have minimal effects on atrial tissue. Class Ib drugs do not block potassium channels directly. Class Ib drugs are used for the suppression of ventricular arrhythmias (ventricular premature beats, ventricular tachycardia, ventricular fibrillation).

Class Ic antiarrhythmic drugs

Class Ic drugs have slow kinetics; they express their electrophysiologic effects at all heart rates. Thus, an ECG obtained during normal rhythm at normal heart rates usually shows fast-channel tissue conduction slowing. Class Ic drugs are more potent antiarrhythmics than either class Ia or class Ib drugs. Class Ic drugs do not block potassium channels directly. Class Ic drugs may organize and slow atrial tachyarrhythmias enough to permit 1:1 AV conduction with marked acceleration of the ventricular response rate. Class Ic drugs are used for suppression of atrial premature beats, ventricular premature beats, supraventricular tachycardia, ventricular tachycardias, atrial fibrillation, atrial flutter, and ventricular fibrillation.

Class II Antiarrhythmic Drugs Class II antiarrhythmic drugs are

Beta-blockers

Beta-blockers affect predominantly slow-channel tissues (sinoatrial and atrioventricular nodes), where they decrease rate of automaticity, slow conduction velocity, and prolong refractoriness. Thus, heart rate is slowed, the PR interval is lengthened, and the AV node transmits rapid atrial depolarizations at a lower frequency.

Class II drugs are used primarily to treat supraventricular tachycardias, including sinus tachycardia, AV nodal re-entry, atrial fibrillation, and atrial flutter. These drugs are also used to treat ventricular tachycardia to raise the threshold for ventricular fibrillation and reduce the ventricular proarrhythmic effects of beta-adrenoceptor stimulation. Beta-blockers are generally well tolerated; adverse effects include lassitude, sleep disturbance, and gastrointestinal upset. These drugs are contraindicated in patients with asthma.

Class III Antiarrhythmic Drugs Class III drugs are Membrane stabilizing drugs, primarily potassium channel blockers. Class III drugs prolong action potential duration and refractoriness in slow- and fast- channel tissues. Thus, the capacity of all cardiac tissues to transmit impulses at high frequencies is reduced, but conduction velocity is not significantly affected. Because the action potential is prolonged, rate of automaticity is reduced. The predominant effect on the ECG is QT-interval prolongation. These drugs are used to treat SVTs and VTs. Class III drugs have a risk of ventricular proarrhythmic, particularly torsade's de pointes VT and are not used in patients with torsade's de pointes VT.

Class IV drugs are Non-dihydropyridine calcium channel blockers. These drugs depress calcium-dependent action potentials in slow-channel tissues and thus decrease the rate of automaticity, slow conduction velocity, and prolong refractoriness. Heart rate is

slowed, the PR interval is lengthened, and the AV node transmits rapid atrial depolarizations at a lower frequency. These drugs are used primarily to treat SVTs. They may also be used to slow rapid atrial fibrillation or atrial flutter. One form of VT (left septal or Belhassen VT) can be treated with verapamil.

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UNIT – V Endocrine Pharmacology – SMB203

V. Endocrine Pharmacology

Endocrine Pharmacology:

Diabetes Mellitus- Insulin – types of insulin, methods to insulin delivery, management of acute complication of diabetes, oral hypoglycemic drugs- classification of drugs and side effect. Diabetes is a set of related diseases in which the body cannot regulate the amount of sugar (specifically, glucose) in the blood.What are the types of diabetes? The related diseases of diabetes include:Type 1 diabetes Type 2 diabetes Gestational diabetes Prediabetes Metabolic syndrome (syndrome X) Insulin resistance (a condition that precedes the development of type 2 diabetes)

What are the symptoms of diabetes?

- Symptoms of diabetes include Increased urine output Excessive hunger
- Urinary tract infections (UTIs) Unexplained weight loss Excessive thirst
- Excessive urination Excessive eating Poor wound healing
- Some types of infection Altered mental status
- Blurry vision Thyroid hormone and Thyroid inhibitors-

What are examples of insulin preparations available?

Insulin preparations Examples of rapid acting insulin

Apidra (insulin glulisine): Supplied in a cartridge, vial, prefilled pen (Solostar) Novolog (insulin aspart): Supplied in a cartridge, vial, prefilled pen (FlexPen) Humalog: (insulin lispro): Supplied in a cartridge, vial, prefilled pen (Kwik Pen) Examples of short acting insulin

Novolin R, Humulin R (regular insulin): Supplied in a vial

Velosulin (insulin with a phosphate buffer): Supplied in a pump device Examples of intermediate acting insulin

Humulin N, Novolin N (NPH): Supplied in a vial, pen (Humulin N pen) Examples of long acting insulin

Lantus (insulin glargine): Supplied in a vial, cartridge (OptiClick), prefilled pen (Solostar)

Levemir (insulin detemir): Supplied in a vial, prefilled pen (FlexPen)

Tresiba (deglutec injection): Supplied in a vial For what type of diabetes is insulin prescribed? Indications for insulin

Type 1 diabetes

Type 2 diabetes Insulin resistance

Diabetic ketoacidosis (DKA) Gestational diabetes

Diabetes treatment during pregnancy

What are the side effects of insulin?

Hypoglycemia, headache, flu like symptoms, weight gain and rash. What is the dosage and how is insulin administrated?

Dosage and Administration of insulin

A meal should be consumed within 30 minutes after administering regular insulin

Insulin usually is administered by subcutaneous injection into the abdominal wall, thigh, buttocks (gluteal region), or upper arm. Injection sites should be rotated within the same region.

Some insulins (for example, regular insulin) also may be administered intravenously.

The dose is individualized for each patient.

A combination of short or rapid acting and intermediate or long acting insulin typically are used. Some patients may develop resistance to insulin and require increasing doses.

Multiple daily insulin injections or continuous subcutaneous infusions via a pump closely mimic pancreatic insulin secretion.

Insulin sliding scales (doses of insulin that are based on the glucose level) may be used for managing critically ill hospitalized patients.
What are the contraindications, warnings, and precautions for insulin? Contraindications
Hypoglycemia (low blood sugar)
Hypersensitivity to insulin or its excipients (inactive co-ingredients) Warnings and Precautions
Hypoglycemia may occur and is the most common side effect of insulin treatment. Severe, life-threatening allergic reactions, including anaphylaxis, may occur.
Hypokalemia (low blood potassium) may occur because insulin stimulates movement of potassium from blood into cells. Combining insulin with potassium-lowering drugs may increase the risk of hypokalemia.
Hepatic (liver) impairment may reduce the insulin requirement. Renal (kidney) dysfunction may reduce the insulin requirement.
Illness, emotional disturbance, or other stress may alter the insulin requirement. Intravenous administration increases the risk of hypoglycemia and hypokalemia. How well does insulin treat diabetes?
Efficacy of insulin
In a 24 week study of patients with type 1 diabetes, regular human subcutaneous insulin (mean dose = 18.3 IU) before breakfast and dinner plus human insulin isophane suspension twice daily (mean dose = 37.1 IU) reduced HbA1c by 0.4% from baseline and fasting glucose by -6 mg/dl.
In a 24 week study of patients with type 2 diabetes, regular human subcutaneous insulin (mean dose = 25.5 IU) before breakfast and dinner plus human insulin isophane suspension twice daily (mean dose = 52.3 IU) reduced HbA1c by 0.6% from baseline and fasting glucose by -6 mg/dl.
What is the mechanism of action (how it works) for insulin?
Pharmacology (mechanism of action) of insulin
Insulin is a hormone secreted by the pancreas. It regulates the movement of glucose from blood into cells. Insulin lowers blood glucose by stimulating peripheral glucose uptake primarily by skeletal muscle cells and fat, and by inhibiting glucose production and release by the liver. Insulin inhibits lipolysis (breakdown of fat), proteolysis (breakdown of proteins), and gluconeogenesis (manufacture of glucose). It also increases protein synthesis and conversion of excess glucose into fat. Insulins used to treat diabetes are pharmacologically similar to the naturally produced hormone. Patients with diabetes are insensitive to insulin and do not produce enough insulin which leads to hyperglycemia and symptoms of diabetes. Exogenous insulin preparations replace insulin in diabetics, increasing the uptake of glucose by cells and reducing the short and long term consequences of diabetes.
Summary
There are a variety of types and preparations of insulin for the treatment of type 1 and type 2 diabetes, gestational diabetes, diabetes during pregnancy, metabolic syndrome, and insulin resistance. Human insulin preparations and regular insulin are made by recombinant DNA technology. Examples of preparations of insulin include rapid acting insulin (Apirda, Novolog, Humalog), short acting insulin (Novolin R, Humulin R), intermediate acting insulin (Humulin N, Novolin N, and long lasting insulin (Lantus, Levemir). Common side effects of insulin include hypoglycemia, headache, weight gain, rash, itching, flu-like symptoms, lipoatrophy, and reaction at the site of injection. Warnings, precautions, and drug interactions should be reviewed prior to taking insulin.
Anatomy & physiology of thyroid gland, classification of drugs and side effect

A butterfly-shaped organ, the thyroid gland is located anterior to the trachea, just inferior to the larynx (Figure 1). The medial region, called the isthmus, is flanked by wing-shaped left and right lobes. Each of the thyroid lobes are embedded with parathyroid glands, primarily on their posterior surfaces. The tissue of the thyroid gland is composed mostly of thyroid follicles. The follicles are made up of a central cavity filled with a sticky fluid called colloid. Surrounded by a wall of epithelial follicle cells, the colloid is the center of thyroid hormone production, and that production is dependent on the hormones' essential and unique component: iodine.SYNTHESIS AND RELEASE OF THYROID HORMONES

Hormones are produced in the colloid when atoms of the mineral iodine attach to a glycoprotein, called thyroglobulin, that is secreted into the colloid by the follicle cells. The following steps outline the hormones' assembly:

Binding of TSH to its receptors in the follicle cells of the thyroid gland causes the cells to actively transport iodide ions (I–) across their cell membrane, from the bloodstream into the cytosol. As a result, the concentration of iodide ions "trapped" in the follicular cells is many times higher than the concentration in the bloodstream.

Iodide ions then move to the lumen of the follicle cells that border the colloid. There, the ions undergo oxidation (their negatively charged electrons are removed). The oxidation of two iodide ions (2 I–) results in iodine (I2), which passes through the follicle cell membrane into the colloid.

In the colloid, peroxidase enzymes link the iodine to the tyrosine amino acids in thyroglobulin to produce two intermediaries: a tyrosine attached to one iodine and a tyrosine attached to two iodines. When one of each of these intermediaries is linked by covalent bonds, the resulting compound is triiodothyronine (T3), a thyroid hormone with three iodines. Much more commonly, two copies of the second intermediary bond, forming tetraiodothyronine, also known as thyroxine (T4), a thyroid hormone with four iodines.

These hormones remain in the colloid center of the thyroid follicles until TSH stimulates endocytosis of colloid back into the follicle cells. There, lysosomal enzymes break apart the thyroglobulin colloid, releasing free T3 and T4, which diffuse across the follicle cell membrane and enter the bloodstream.

In the bloodstream, less than one percent of the circulating T3 and T4 remains unbound. This free T3 and T4 can cross the lipid bilayer of cell membranes and be taken up by cells. The remaining 99 percent of circulating T3 and T4 is bound to specialized transport proteins called thyroxine-binding globulins (TBGs), to albumin, or to other plasma proteins. This "packaging" prevents their free diffusion into body cells. When blood levels of T3 and T4 begin to decline, bound T3 and T4 are released from these plasma proteins and readily cross the membrane of target cells. T3 is more potent than T4, and many cells convert T4 to T3 through the removal of an iodine atom.

REGULATION OF TH SYNTHESIS

The release of T3 and T4 from the thyroid gland is regulated by thyroid-stimulating hormone (TSH). As shown in Figure 2, low blood levels of T3 and T4 stimulate the release of thyrotropin-releasing hormone (TRH) from the hypothalamus, which triggers secretion of TSH from the anterior pituitary. In turn, TSH stimulates the thyroid gland to secrete T3 and T4. The levels of TRH, TSH, T3, and T4 are regulated by a negative feedback system in which increasing levels of T3 and T4 decrease the production and secretion of TSH.

FUNCTIONS OF THYROID HORMONES

The thyroid hormones, T3 and T4, are often referred to as metabolic hormones because their levels influence the body's basal metabolic rate, the amount of energy used by the body at rest. When T3 and T4 bind to intracellular receptors located on the mitochondria, they cause an increase in nutrient breakdown and the use of oxygen to produce ATP. In addition, T3

and T4 initiate the transcription of genes involved in glucose oxidation. Although these mechanisms prompt cells to produce more ATP, the process is inefficient, and an abnormally increased level of heat is released as a byproduct of these reactions. This so-called calorigenic effect (calor- = "heat") raises body temperature.

Adequate levels of thyroid hormones are also required for protein synthesis and for fetal and childhood tissue development and growth. They are especially critical for normal development of the nervous system both in utero and in early childhood, and they continue to support neurological function in adults. As noted earlier, these thyroid hormones have a complex interrelationship with reproductive hormones, and deficiencies can influence libido, fertility, and other aspects of reproductive function. Finally, thyroid hormones increase the body's sensitivity to catecholamines (epinephrine and norepinephrine) from the adrenal medulla by upregulation of receptors in the blood vessels. When levels of T3 and T4 hormones are excessive, this effect accelerates the heart rate, strengthens the heartbeat, and increases blood pressure. Because thyroid hormones regulate metabolism, heat production, protein synthesis, and many other body functions, thyroid disorders can have severe and widespread consequences.

Disorders of the Endocrine System: Iodine Deficiency, Hypothyroidism, and Hyperthyroidism

As discussed above, dietary iodine is required for the synthesis of T3 and T4. But for much of the world's population, foods do not provide adequate levels of this mineral, because the amount varies according to the level in the soil in which the food was grown, as well as the irrigation and fertilizers used. Marine fish and shrimp tend to have high levels because they concentrate iodine from seawater, but many people in landlocked regions lack access to seafood. Thus, the primary source of dietary iodine in many countries is iodized salt.

Fortification of salt with iodine began in the United States in 1924, and international efforts to iodize salt in the world's poorest nations continue today.

Dietary iodine deficiency can result in the impaired ability to synthesize T3 and T4, leading to a variety of severe disorders. When T3 and T4 cannot be produced, TSH is secreted in increasing amounts. As a result of this hyperstimulation, thyroglobulin accumulates in the thyroid gland follicles, increasing their deposits of colloid. The accumulation of colloid increases the overall size of the thyroid gland, a condition called a goiter (Figure 3). A goiter is only a visible indication of the deficiency. Other iodine deficiency disorders include impaired growth and development, decreased fertility, and prenatal and infant death. Moreover, iodine deficiency is the primary cause of preventable mental retardation worldwide. Neonatal hypothyroidism (cretinism) is characterized by cognitive deficits, short stature, and sometimes deafness and muteness in children and adults born to mothers who were iodine-deficient during pregnancy.

In areas of the world with access to iodized salt, dietary deficiency is rare. Instead, inflammation of the thyroid gland is the more common cause of low blood levels of thyroid hormones. Called hypothyroidism, the condition is characterized by a low metabolic rate, weight gain, cold extremities, constipation, reduced libido, menstrual irregularities, and reduced mental activity. In contrast, hyperthyroidism—an abnormally elevated blood level of thyroid hormones—is often caused by a pituitary or thyroid tumor. In Graves' disease, the hyperthyroid state results from an autoimmune reaction in which antibodies overstimulate the follicle cells of the thyroid gland. Hyperthyroidism can lead to an increased metabolic rate, excessive body heat and sweating, diarrhea, weight loss, tremors,

and increased heart rate. The person's eyes may bulge (called exophthalmos) as antibodies produce inflammation in the soft tissues of the orbits. The person may also develop a goiter.

CALCITONIN
The thyroid gland also secretes a hormone called calcitonin that is produced by the parafollicular cells (also called C cells) that stud the tissue between distinct follicles. Calcitonin is released in response to a rise in blood calcium levels. It appears to have a function in decreasing blood calcium concentrations by:

Inhibiting the activity of osteoclasts, bone cells that release calcium into the circulation by degrading bone matrix

Increasing osteoblastic activity
Decreasing calcium absorption in the intestines Increasing calcium loss in the urine
However, these functions are usually not significant in maintaining calcium homeostasis, so the importance of calcitonin is not entirely understood. Pharmaceutical preparations of calcitonin are sometimes prescribed to reduce osteoclast activity in people with osteoporosis and to reduce the degradation of cartilage in people with osteoarthritis. The hormones secreted by thyroid are summarized in Table 4.

Of course, calcium is critical for many other biological processes. It is a second messenger in many signaling pathways, and is essential for muscle contraction, nerve impulse transmission, and blood clotting. Given these roles, it is not surprising that blood calcium levels are tightly regulated by the endocrine system. The organs involved in the regulation are the parathyroid glands.
Drug Classes HormonesThyroid Drugs Print Share
Thyroid drugs
Medically reviewed by C. Fookes, BPharm Last updated on Feb 5, 2019.

What are Thyroid drugs?
Thyroid drugs (thyroid hormones) are used to supplement low thyroid levels in people with hypothyroidism.

Hypothyroidism is a condition in which the thyroid gland does not produce enough thyroid hormones to meet the needs of the body. Doctors may use the term "an underactive thyroid gland" to describe hypothyroidism.

Thyroid hormone and Thyroid inhibitors- Anatomy & physiology of thyroid gland, classification of drugs and side effect

Our thyroid gland is a butterfly-shaped gland that is located just below the Adam's apple, along the front of the windpipe. Even though thyroid hormones are made in the thyroid gland, the production of these hormones is regulated by another hormone, called thyroid stimulating hormone (TSH), which is made by the pituitary gland (a pea-shaped organ found at the base

of the brain). If thyroid hormone levels are low, then our metabolism and many other body functions slow down.

Another condition, called hyperthyroidism, is when the thyroid produces too much thyroid hormone. Although hyperthyroidism seems to be the opposite of hypothyroidism, the link between them is complex, and one can lead to the other in certain circumstances.

What are thyroid drugs used for?
Thyroid drugs are used to treat hypothyroidism, also referred to as an underactive thyroid.

Even though the thyroid produces two hormones, T3 and T4, T4 is most commonly prescribed to treat hypothyroidism.

The only way to test for hypothyroidism is with a blood test, as symptoms vary significantly between people and are similar to several other conditions.

Symptoms of hypothyroidism include:

Cold intolerance Constipation Decreased sweating Dry skin
Frequent urinary and respiratory tract infections Heavy periods
Joint and muscle pain, cramps, or weakness; slowed movements Loss of sex drive
Puffy face, feet, and hands Sleeplessness (insomnia) Slowed heart rate
Thin brittle hair or fingernails Tiredness and fatigue
Weight gain.
What are the differences between thyroid drugs?
Thyroid hormone preparations can be divided into two categories:

Natural preparations derived from animal thyroid Synthetic preparations manufactured in a laboratory.
Natural preparations include desiccated thyroid and thyroglobulin.

The most common medication used for supplementation is synthetic thyroxine, also called levothyroxine. This is identical to the T4 hormone. T4 is converted into T3 in the body.

Liothyronine (T3, also called triiodothyronine) is another thyroid hormone that may be prescribed to people who are unable to properly convert T4 into T3.

Liotrix is a combination of levothyroxine (T4) and liothyronine (T3) in a 4:1 ratio. Although the ratio remains the same, there are multiple strengths of this medication, so ensure you receive the correct dose.

Ingredients Brand name examples
levothyroxine Levoxyl, Synthroid, Tirosint, Unithroid liothyronine Cytomel, Triostat
liotrix Thyrolar-1 (also 1/4, ½, 2,3) thyroid desiccated Armour-thyroid
It is important that levothyroxine is taken on an empty stomach at least 30 to 60 minutes before breakfast to ensure that it is absorbed properly. It should be taken with a big glass of

water, and spaced apart by at least four hours from antacids or supplements such as calcium or iron.

Are thyroid drugs safe?
Thyroid medicines are safe when taken at the recommended dose and prescribed by a doctor. You must ONLY take what your doctor recommends. The correct dosage for you is based on your age, health, current natural thyroid hormone levels, and weight.

When you first start treatment for hypothyroidism, your doctor will regularly monitor the levels of different thyroid hormones in your blood to determine if your dosage of thyroid medication needs adjusting. Once the correct dosage has been established for you, the frequency of these blood tests will decrease. Thyroid drugs are generally taken for life.

It will take a few months for your thyroid levels to get back to normal but as long as you are taking your thyroid drugs as prescribed, then you should not have many side effects. Side effects generally happen because you are taking too much thyroid hormone.

Thyroid hormones should NEVER be taken by people without thyroid problems to treat obesity or for weight loss. Some fatalities have occurred when they have been used if these drugs are taken in large dosages for this indication.

Be aware that some supplements marketed as supporting thyroid health may actually contain undisclosed thyroid hormones. Taking these in addition to your thyroid medications may cause toxicity. Thyroid drugs have also been serendipitously added to supplements labeled as only containing animal tissue or herbs such as ashwagandha, guggul, and Coleus forskohlii. Even seaweed-containing products, such as kelp, contain high levels of iodine which can interfere with thyroid function. If you are taking thyroid drugs, always talk with your doctor before taking any supplement.

Also, talk to your doctor about your diet. Some people with hypothyroidism are particularly sensitive to the effects of iodine, and it may trigger or worsen hypothyroidism. In addition, high fiber diets and certain types of foods such as soy or cruciferous vegetables may affect how your body responds to thyroid drugs.

What are the side effects of thyroid drugs?
Thyroid drugs don’t tend to cause side effects if taken at the right dose. Side effects are an indication that you may be taking too much thyroid hormone and may include:

A fast heartbeat Difficulty sleeping
Dull, lifeless, or brittle hair Heat sensitivity
Hunger
Nervousness or anxiety Shakiness
Sweating

Tiredness Weight loss.
If you develop any of these side effects talk to your doctor about a blood test to check your thyroid hormone levels.

Drug Classes HormonesThyroid Drugs Print Share
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Puffy face, feet, and hands Sleeplessness (insomnia) Slowed heart rate
Thin brittle hair or fingernails Tiredness and fatigue
Weight gain.

If hypothyroidism develops in children or teenagers it may affect their growth; interfere with learning and brain development; and delay tooth development and puberty.

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Dull, lifeless, or brittle hair Heat sensitivity
Hunger
Nervousness or anxiety Shakiness
Sweating Tiredness Weight loss.
If you develop any of these side effects talk to your doctor about a blood test to check your thyroid hormone levels.

List of Thyroid drugs:

Drug name: Westhroid, Generic name: thyroid desiccated Levo-T Generic name: levothyroxine
Armour Thyroid (Pro)Generic name: thyroid desiccated Cytomel (Pro) Generic name: liothyronine
Levoxyl (Pro) Generic name: levothyroxine Tirosint (Pro) Generic name: levothyroxine
Nature-ThroidGeneric name: thyroid desiccated Levothroid (Pro) Generic name: levothyroxine
Drug name: Synthroid (Pro) Generic name: levothyroxine

WP Thyroid Generic name: thyroid desiccated Unithroid (Pro) Generic name: levothyroxine
NP Thyroid (Pro) Generic name: thyroid desiccated Euthyrox (Pro) Generic name: levothyroxine
Thyrogen (Pro) Generic name: thyrotropin alpha

Corticosteroids- Anatomy & physiology of adrenal gland, classification of drugs and side effect

The adrenal glands are wedges of glandular and neuroendocrine tissue adhering to the top of the kidneys by a fibrous capsule (Figure 1). The adrenal glands have a rich blood supply and experience one of the highest rates of blood flow in the body. They are served by several arteries branching off the aorta, including the suprarenal and renal arteries. Blood flows to each adrenal gland at the adrenal cortex and then drains into the adrenal medulla. Adrenal hormones are released into the circulation via the left and right suprarenal veins.

This diagram shows the left adrenal gland located atop the left kidney. The gland is composed of an outer cortex and an inner medulla all surrounded by a connective tissue capsule. The cortex can be subdivided into additional zones, all of which produce different types of hormones. The outermost layer is the zona glomerulosa, which releases mineralcorticoids, such as aldosterone, that regulate mineral balance. Underneath this layer is the zona fasciculate, which releases glucocorticoids, such as cortisol, corticosterone and cortisone, that regulate glucose metabolism. Underneath this layer is the zona reticularis, which releases androgens, such as dehydroepiandrosterone, that stimulate masculinization. Below this layer is the adrenal medulla, which releases stress hormones, such as epinephrine and norepinephrine, that stimulate the symphathetic ANS.
Figure 1. Adrenal Glands. Both adrenal glands sit atop the kidneys and are composed of an outer cortex and an inner medulla, all surrounded by a connective tissue capsule. The cortex can be subdivided into additional zones, all of which produce different types of hormones. LM × 204. (Micrograph provided by the Regents of University of Michigan Medical School © 2012)
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View the University of Michigan WebScope at http://141.214.65.171/Histology/Endocrine%20System/New%20Scans/230_HISTO_40x.svs/ view.apml to explore the tissue sample in greater detail.

The adrenal gland consists of an outer cortex of glandular tissue and an inner medulla of nervous tissue. The cortex itself is divided into three zones: the zona glomerulosa, the zona fasciculata, and the zona reticularis. Each region secretes its own set of hormones.

The adrenal cortex, as a component of the hypothalamic-pituitary-adrenal (HPA) axis, secretes steroid hormones important for the regulation of the long-term stress response, blood pressure and blood volume, nutrient uptake and storage, fluid and electrolyte balance, and inflammation. The HPA axis involves the stimulation of hormone release of adrenocorticotropic hormone (ACTH) from the pituitary by the hypothalamus. ACTH then stimulates the adrenal cortex to produce the hormone cortisol. This pathway will be discussed in more detail below.

The adrenal medulla is neuroendocrine tissue composed of postganglionic sympathetic nervous system (SNS) neurons. It is really an extension of the autonomic nervous system, which regulates homeostasis in the body. The sympathomedullary (SAM) pathway involves the stimulation of the medulla by impulses from the hypothalamus via neurons from the thoracic spinal cord. The medulla is stimulated to secrete the amine hormones epinephrine and norepinephrine.

One of the major functions of the adrenal gland is to respond to stress. Stress can be either physical or psychological or both. Physical stresses include exposing the body to injury, walking outside in cold and wet conditions without a coat on, or malnutrition. Psychological stresses include the perception of a physical threat, a fight with a loved one, or just a bad day at school.

The body responds in different ways to short-term stress and long-term stress following a pattern known as the general adaptation syndrome (GAS). Stage one of GAS is called the alarm reaction. This is short-term stress, the fight-or-flight response, mediated by the hormones epinephrine and norepinephrine from the adrenal medulla via the SAM pathway. Their function is to prepare the body for extreme physical exertion. Once this stress is relieved, the body quickly returns to normal. The section on the adrenal medulla covers this response in more detail.

If the stress is not soon relieved, the body adapts to the stress in the second stage called the stage of resistance. If a person is starving for example, the body may send signals to the gastrointestinal tract to maximize the absorption of nutrients from food.

If the stress continues for a longer term however, the body responds with symptoms quite different than the fight-or-flight response. During the stage of exhaustion, individuals may begin to suffer depression, the suppression of their immune response, severe fatigue, or even a fatal heart attack. These symptoms are mediated by the hormones of the adrenal cortex, especially cortisol, released as a result of signals from the HPA axis.

Adrenal hormones also have several non–stress-related functions, including the increase of blood sodium and glucose levels, which will be described in detail below.

ADRENAL CORTEX

The adrenal cortex consists of multiple layers of lipid-storing cells that occur in three structurally distinct regions. Each of these regions produces different hormones.

QR Code representing a URL

Visit this link to view an animation describing the location and function of the adrenal glands. Visit this link to view an animation describing the location and function of the adrenal glands. Which hormone produced by the adrenal glands is responsible for the mobilization of energy stores?

HORMONES OF THE ZONA GLOMERULOSA

The most superficial region of the adrenal cortex is the zona glomerulosa, which produces a group of hormones collectively referred to as mineralocorticoids because of their effect on body minerals, especially sodium and potassium. These hormones are essential for fluid and electrolyte balance.

Aldosterone is the major mineralocorticoid. It is important in the regulation of the concentration of sodium and potassium ions in urine, sweat, and saliva. For example, it is released in response to elevated blood K+, low blood Na+, low blood pressure, or low blood volume. In response, aldosterone increases the excretion of K+ and the retention of Na+,

which in turn increases blood volume and blood pressure. Its secretion is prompted when CRH from the hypothalamus triggers ACTH release from the anterior pituitary.

Aldosterone is also a key component of the renin-angiotensin-aldosterone system (RAAS) in which specialized cells of the kidneys secrete the enzyme renin in response to low blood volume or low blood pressure. Renin then catalyzes the conversion of the blood protein angiotensinogen, produced by the liver, to the hormone angiotensin I. Angiotensin I is converted in the lungs to angiotensin II by angiotensin-converting enzyme (ACE). Angiotensin II has three major functions:

Initiating vasoconstriction of the arterioles, decreasing blood flow
Stimulating kidney tubules to reabsorb NaCl and water, increasing blood volume
Signaling the adrenal cortex to secrete aldosterone, the effects of which further contribute to fluid retention, restoring blood pressure and blood volume
For individuals with hypertension, or high blood pressure, drugs are available that block the production of angiotensin II. These drugs, known as ACE inhibitors, block the ACE enzyme from converting angiotensin I to angiotensin II, thus mitigating the latter's ability to increase blood pressure.

HORMONES OF THE ZONA FASCICULATA
The intermediate region of the adrenal cortex is the zona fasciculata, named as such because the cells form small fascicles (bundles) separated by tiny blood vessels. The cells of the zona fasciculata produce hormones called glucocorticoids because of their role in glucose metabolism. The most important of these is cortisol, some of which the liver converts to cortisone. A glucocorticoid produced in much smaller amounts is corticosterone. In response to long-term stressors, the hypothalamus secretes CRH, which in turn triggers the release of ACTH by the anterior pituitary. ACTH triggers the release of the glucocorticoids. Their overall effect is to inhibit tissue building while stimulating the breakdown of stored nutrients to maintain adequate fuel supplies. In conditions of long-term stress, for example, cortisol promotes the catabolism of glycogen to glucose, the catabolism of stored triglycerides into fatty acids and glycerol, and the catabolism of muscle proteins into amino acids. These raw materials can then be used to synthesize additional glucose and ketones for use as body fuels. The hippocampus, which is part of the temporal lobe of the cerebral cortices and important in

memory formation, is highly sensitive to stress levels because of its many glucocorticoid receptors.

You are probably familiar with prescription and over-the-counter medications containing glucocorticoids, such as cortisone injections into inflamed joints, prednisone tablets and steroid-based inhalers used to manage severe asthma, and hydrocortisone creams applied to relieve itchy skin rashes. These drugs reflect another role of cortisol—the downregulation of the immune system, which inhibits the inflammatory response.

HORMONES OF THE ZONA RETICULARIS
The deepest region of the adrenal cortex is the zona reticularis, which produces small amounts of a class of steroid sex hormones called androgens. During puberty and most of adulthood, androgens are produced in the gonads. The androgens produced in the zona reticularis supplement the gonadal androgens. They are produced in response to ACTH from

the anterior pituitary and are converted in the tissues to testosterone or estrogens. In adult women, they may contribute to the sex drive, but their function in adult men is not well understood. In post-menopausal women, as the functions of the ovaries decline, the main source of estrogens becomes the androgens produced by the zona reticularis.

ADRENAL MEDULLA

As noted earlier, the adrenal cortex releases glucocorticoids in response to long-term stress such as severe illness. In contrast, the adrenal medulla releases its hormones in response to acute, short-term stress mediated by the sympathetic nervous system (SNS).

The medullary tissue is composed of unique postganglionic SNS neurons called chromaffin cells, which are large and irregularly shaped, and produce the neurotransmitters epinephrine (also called adrenaline) and norepinephrine (or noradrenaline). Epinephrine is produced in greater quantities—approximately a 4 to 1 ratio with norepinephrine—and is the more powerful hormone. Because the chromaffin cells release epinephrine and norepinephrine into the systemic circulation, where they travel widely and exert effects on distant cells, they are considered hormones. Derived from the amino acid tyrosine, they are chemically classified as catecholamines.

The secretion of medullary epinephrine and norepinephrine is controlled by a neural pathway that originates from the hypothalamus in response to danger or stress (the SAM pathway). Both epinephrine and norepinephrine signal the liver and skeletal muscle cells to convert glycogen into glucose, resulting in increased blood glucose levels. These hormones increase the heart rate, pulse, and blood pressure to prepare the body to fight the perceived threat or flee from it. In addition, the pathway dilates the airways, raising blood oxygen levels. It also prompts vasodilation, further increasing the oxygenation of important organs such as the lungs, brain, heart, and skeletal muscle. At the same time, it triggers vasoconstriction to blood vessels serving less essential organs such as the gastrointestinal tract, kidneys, and skin, and downregulates some components of the immune system. Other effects include a dry mouth, loss of appetite, pupil dilation, and a loss of peripheral vision. The major hormones of the adrenal glands are summarized in Table 5.

Hormones of the Adrenal Glands

Adrenal gland Associated hormones Chemical class Effect Adrenal cortexAldosterone Steroid Increases blood Na+ levels

Adrenal cortexCortisol, corticosterone, cortisone Steroid Increase blood glucose levels

Adrenal medulla Epinephrine, norepinephrine Amine Stimulate fight-or-flight response

DISORDERS INVOLVING THE ADRENAL GLANDS

Several disorders are caused by the dysregulation of the hormones produced by the adrenal glands. For example, Cushing's disease is a disorder characterized by high blood glucose levels and the accumulation of lipid deposits on the face and neck. It is caused by hypersecretion of cortisol. The most common source of Cushing's disease is a pituitary tumor that secretes cortisol or ACTH in abnormally high amounts. Other common signs of Cushing's disease include the development of a moon-shaped face, a buffalo hump on the back of the neck, rapid weight gain, and hair loss. Chronically elevated glucose levels are also associated with an elevated risk of developing type 2 diabetes. In addition to hyperglycemia, chronically elevated glucocorticoids compromise immunity, resistance to infection, and memory, and can result in rapid weight gain and hair loss.

In contrast, the hyposecretion of corticosteroids can result in Addison's disease, a rare disorder that causes low blood glucose levels and low blood sodium levels. The signs and symptoms of Addison's disease are vague and are typical of other disorders as well, making

diagnosis difficult. They may include general weakness, abdominal pain, weight loss, nausea, vomiting, sweating, and cravings for salty food.
MedicineNet NEWSLETTERS SYMPTOM CHECKER

home/corticosteroids-oral article

Corticosteroids Drugs: Systemic, Oral, Injections, and Types
What are corticosteroids? What is the mechanism of action (how do they work)? What are some examples of systemic (oral and injectable) corticosteroids?
What are corticosteroids used for?
What are the side effects of systemic corticosteroids?
What are the differences between the types of systemic corticosteroids? What drugs interact (contraindications) with corticosteroids?
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Moderate to Severe Forms of Psoriasis Slideshow
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What are corticosteroids? What is the mechanism of action (how do they work)? Corticosteroids are steroid hormones that are either produced by the body or are man-made.

Systemic corticosteroids refer to corticosteroids that are given orally or by injection and distribute throughout the body. It does not include corticosteroids used in the eyes, ears, or

nose, on the skin or that are inhaled, although small amounts of these corticosteroids can be absorbed into the body.

Naturally occurring corticosteroids, hydrocortisone (Cortef) and cortisone, are produced by the outer portion of the adrenal gland known as the cortex (hence the name, corticosteroid). Corticosteroids are classified as either:

glucocorticoids (anti-inflammatory) which suppress inflammation and immunity and assist in the breakdown of fats, carbohydrates, and proteins, or as
mineralocorticoids (salt retaining) that regulate the balance of salt and water in the body. Synthetic corticosteroids mimic the actions of naturally occurring corticosteroids and may be used to replace corticosteroids in people with adrenal glands that are unable to produce

adequate amounts of corticosteroids, however, they more often are used in higher-than-replacement doses to treat diseases of immunity, inflammation or salt and water balance.

Examples of synthetic corticosteroids include:

bethamethasone, (Celestone) prednisone (Prednisone Intensol) prednisolone (Orapred, Prelone)
triamcinolone (Aristospan Intra-Articular, AristospanIntralesional, Kenalog) methylprednisolone (Medrol, Depo-Medrol, Solu-Medrol)
dexamethasone (Dexamethasone Intensol, DexPak 10 Day, DexPak 13 Day, DexPak 6 Day).
Some glucocorticoids also in addition to their anti-inflammatory actions have salt retaining properties but they are used mostly for their anti-inflammatory effects. Fludrocortisone (Florinef), a synthetic mineralocorticoid has strong salt retaining effects with significant anti- inflammatory actions, and is used mostly for it's salt retaining capabilities.

What are some examples of systemic (oral and injectable) corticosteroids?
The following is a list of the systemic (oral and injectable) corticosteroids that are available in the United States:

Glucocorticoids:

hydrocortisone (Cortef) cortisone
ethamethasoneb (Celestone) prednisone (Prednisone Intensol) prednisolone (Orapred, Prelone)
triamcinolone (Aristospan Intra-Articular, AristospanIntralesional, Kenalog) Methylprednisolone (Medrol, Depo-Medrol, Solu-Medrol)
dexamethasone (Dexamethasone Intensol, DexPak 10 Day, DexPak 13 Day, DexPak 6 Day)
Mineralocorticoid:

Fludrocortisone (Florinef)
List of 6 Common Asthma Medications
Asthma medications come in the form of pills, inhalers, and nebulizers. Examples of asthma medications include:

Inhalers and nebulizers

fluticasone (Flovent and ArnuityEllipta) budesonide (Pulmicort)
Combination controller inhaled medications that help the airways open.

formoterol salmeterol vilanterol
The combination controller medications include fluticasone/salmeterol (Advair) Click to read more about the types of asthma medications and how they work »

What are corticosteroids used for?

Corticosteroids belonging to the glucocorticoid class influence the body system in several ways, but they are used mostly for their strong anti-inflammatory effects and in conditions that are related to the immune system function such as:

arthritis (for example, rheumatoid arthritis),

colitis (ulcerative colitis, and Crohn's disease), asthma,
bronchitis,
some situations involving skin rashes,
allergic or inflammatory conditions involving the nose and eyes.
Glucocorticoid corticosteroids are used to treat systemic lupus, severe psoriasis, leukemia, lymphomas, idiopathic thrombocytopenic purpura, and autoimmune hemolytic anemia. These corticosteroids also are used to suppress the immune system and prevent rejection in people who have undergone organ transplant as well as many other conditions.

Fludrocortisone (Florinef), a potent systemic oral mineralocorticoid corticosteroid is used to treat Addison's disease and diseases that cause salt loss as in congenital adrenal hyperplasia. It also is used commonly to treat conditions of low blood pressure (hypotension) although this is not a Food and Drug Administration (FDA) approved indication.
What are the side effects of systemic corticosteroids?
Corticosteroids have many side effects that can be mild or serious. These side effects are more apparent when corticosteroids are used at higher doses or for extended periods of time. This section lists only some of these side effects of corticosteroids.

Corticosteroids can:

cause sodium (salt) and fluid to be retained in the body and cause weight gain or swelling of the legs (edema)
High blood pressure Loss of potassium Headache
Muscle weakness
Puffiness of the face (moon face) Facial hair growth
Thinning and easy bruising of the skin Slow wound healing
Glaucoma Cataracts
Ulcers in the stomach and duodenum

Loss of diabetes control Menstrual irregularity
"Buffalo hump," a condition described as a rounding of the upper back
The prolonged use of corticosteroids can cause obesity, growth retardation in children, and even lead to convulsions and psychiatric disturbances. Reported psychiatric disturbances include depression, euphoria, insomnia, mood swings, and personality changes. Psychotic behaviors also have been reported.

Corticosteroids, since they suppress the immune system, can lead to an increase in the rate of infections and reduce the effectiveness of vaccines and antibiotics.

The long term use of corticosteroids may cause osteoporosis which can result in bone fractures.

Shrinking (atrophy) of the adrenal glands can be caused by the long term use of corticosteroids resulting in the body's inability to produce cortisol, the body's natural corticosteroid, when the systemic corticosteroids are discontinued.

Another condition which can result from the long term use of corticosteroids is adrenal necrosis of the hip joints, a very painful and serious condition that may require surgery. Any symptoms of hip or knee pain in people taking corticosteroids require prompt medical attention.

Corticosteroids should not be stopped suddenly after prolonged use as this can result in adrenal crisis because of the body's inability to secrete enough cortisol to make up for the withdrawal. Nausea, vomiting, and shock are the reported side effects of adrenal crisis.
What are the differences between the types of systemic corticosteroids?
Corticosteroids differ in their relative amount of anti-inflammatory and mineralocorticoid potency and they are used according to these effects. Among the systemic (oral and injectable) corticosteroids, fludrocortisone (Florinef) has the most significant mineralocorticoid (salt retaining) actions and is best used for this effect despite it's strong anti-inflammatory action.

Other systemically available corticosteroids have mostly glucocorticoid effects, and are used for their anti-inflammatory activities. Examples of these include the naturally occurring hydrocortisone (Cortef) and cortisone, and the synthetic corticosteroids including:

bethamethasone (Celestone) prednisone (Prednisone Intensol) prednisolone (Orapred, Prelone)
triamcinolone (Aristospan Intra-Articular, AristospanIntralesional, Kenalog) methylprednisolone((Medrol, Depo-Medrol, Solu-Medrol)
dexamethasone (Dexamethasone Intensol, DexPak 10 Day, DexPak 13 Day, DexPak 6 Day).
Among all glucocorticoids, prednisone is not effective in the body unless it is converted to prednisolone by enzymes in the liver. For this reason prednisone may not be very effective in people with liver disease because of a reduction in their ability to convert prednisone to prednisolone.
What drugs interact (contraindications) with corticosteroids?
Certain drugs such as troleandomycin (TAO), erythromycin (Ery-Tab, EryPed 200), and clarithromycin (Biaxin) and ketoconazole (Nizoral) can reduce the ability of the liver to metabolize (breakdown) corticosteroids and this may lead to an increase in the levels and side effects of corticosteroids in the body. On the other hand, phenobarbital, ephedrine, phenytoin (Dilantin), and rifampin (Rifadin, Rimactane) may reduce the blood levels of corticosteroids by increasing the breakdown of corticosteroids by the liver. This may necessitate an increase of corticosteroid dose when they are used in combination with these drugs.

Estrogens have been shown to increase the effects of corticosteroids possibly by decreasing their breakdown by the liver.

Corticosteroid effects on warfarin (Coumadin) can vary; therefore when taking warfarin (Coumadin) along with corticosteroids, there may be increased need for monitoring coagulation levels more closely.

Low blood potassium (hypokalemia) and a higher chance of heart failure can result from combining corticosteroids with drugs that reduce potassium in the blood (for example, diuretics, amphotericin B).

Anticholinesterase drugs (for example, physostigmine) may cause severe weakness in some patients with myasthenia gravis when prescribed with corticosteroids.

Corticosteroids can increase blood glucose, so close monitoring of blood sugar and higher doses of diabetes medications may be needed.

Cholestyramine (Questran, Questran Light) can decrease the absorption of oral corticosteroids from the stomach and this could reduce the blood levels of corticosteroids.

Estrogen, Progestins and Contraceptives- Classification of drugs and side effect, Oxytocin and other drugs acting on uterus- Classification of drugs and side effect,

Since the development and approval of the first combined oral contraceptive (COC) pill, combined estrogen-progestin hormonal contraception (CHC) has evolved from high-dose estrogen formulations (150 mcg) to very low doses (10 and 20 mcg). Simultaneously, dosing mechanisms have expanded to include vaginal rings and the transdermal patch. While most women are candidates for CHC use and do well on them, the safety and side effect profiles must be considered as women balance their long-term need for birth control with the management and treatment of any concurrent medical conditions.
This topic will discuss CHC side effects, common health concerns, and use in women with medical conditions. Where possible, we report research findings by CHC type, though we frequently make recommendations for the CHC patch and ring that are an extrapolation of the oral contraceptive pill data. Detailed information on contraceptive selection and CHC types are presented separately.

Drug affecting calcium balance- Physiology of calcium balance, classification of drugs and side effect.
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Drugs affecting ca++ balance
1. Drugs stimulate bone formation Calcium Preparations •Calcium phosphate/ carbonate/ lactate/ lactobionate/ gluconate/glucobionate •Hydroxyapatite Vitamin D Preparations
• Ergocalciferol (Vit. D2) •Cholecalciferol (Vit. D3) •Calcitriol (1,2,5, (OH)2 D3)
• Alfacalcidol (1 (OH) D3) •Doxercalciferol (1(OH) D2) •Paracalcitol (19 Nor 1,25 (OH) D2) Parathormone Preparations •Drugs increasing calcium levels are useful in:
• Hypocalcemia •Hypoparathyroidism •Rickets •Osteomalacia •Osteoporosis •Teriparatide (Recombinant PTH)
2. Drugs inhibits bone resorption Miscellaneous Calcitonin Cinacalcet Denosumab SERM Gallium nitrate Bisphosphonates •Etidronate •Alendronate •Pamidronate •They are also use in •Hypercalcemia •Paget's disease of bone

Strontium ranelate- process both action(stimulate bone formation + Inhibit bone resorption

3. Normal : 9- 11mg/dL Hypercalcemia > 12 mg/dL Hypocalcaemia < 8 mg/dL 99% of calcium of our body is in bone & teeth Metabolism regulated by -Parathormone(PTH) -Vit-D -calcitonin Ca++ metabolism also Connected to phosphorus + Magnesium metabolism
4. Physiological role of Calcium Controls excitability of nerves & muscles Maintains integrity and regulates permeability of cell membrane Essential for muscle contraction (skeletal ,cardiac) Formation of milk, bone & teeth Necessary for blood coagulation Necessary for release of some neurotransmitters from storage vesicles of the nerve terminal Acts as a second messenger
5. Absorbed by facilitated diffusion & carrier mediated active transport in duodenum Phosphates, Oxalates & tetracycline's complexes calcium in gut & inhibits its absorption Vitamin-D & Parathyroid Ca2+reabsorption calcitonin Ca2+ reabsorption in kidney Absorption & Excretion
6. lcii Preparations of Calcium Calcium chloride (27% calcium) Highly water soluble but (irritant to gastric mucosa) so no use Calcium gluconoate (9% calcium) Nonirritating to GI mucosa preferred for parental route in tetany. Oral preparation Calcium-gluconate Calcium-citrate Calcium-lactate Calcium carbonate Parental preparation Intravenous-calcium gluconate Intravenous calcium chloride
7. lcii Calcium lactate (13% calcium). Oral non-irritant & well tolerated. Calcium dibasic phosphate (23% calcium). Insoluble , React with HCl to form soluble chloride in stomach. Used as antacid & to supplement calcium. Calcium carbonate (40% calcium).-Cheap,tasteless, Preferred because of high percentage of calcium. As a Antacid mainly used
8. 1.Tetany:- In severe cases:- 5-10 ml Ca. gluconate stat followed by slow i/v infusion with total of 0.45- 0.9 gm of calcium Long term Treatment:- with 1-1.5 gm calcium orally daily. 2. Osteoporosis:- Calcium + vit. D along with hormone replacement therapy/ raloxifene/ alendronate will ↓se the rate of Ca2+ loss from the bone. 3.Calcium carbonate:- antacid 4.Iv- calcium gluconate:- use in urticaria,dermatoses 5.Others:- Growing children, pregnant & lactating women Long term corticosteroid therapy After removal of parathyroid tumour Dietary deficiency Postmenopausal osteoporosis
9. . . Young adults 11-24 yrs Pregnant & lactating women Men 25-65 yrs Women 25-50 yrs Women 51-65 yrs if taking hormone replacement therapy 1.2- 1.5 gms Children 1-10 yrs 0.8- 1.2 gms 1.0 gms Women 51-65 yrs not taking HRT everyone › 65 yrs 1.5 gms
10. Adverse effects:- Constipation, Bloating & flatulence, excess gas (especially with Calcium carbonate) have been reported Hypercalcemic hormone. Secreted from chief cell of

parathyroid gland Sandstorm discovered parathyroid gland in 1890 MOA:- PTH receptor is GPCR receptor Activate PTH receptor (+) Adenylyl cyclase cAMP + Ca++ conc.Various effects
11. PTH Hormone Serum Phosphate Serum Ca++ Remark PTH ↓ (due to Increase renal excretion) ↑ (due to increase intestinal absorption and decrease renal execration Excess PTH can result in osteoporosis Action on Bone: - ↑Resorption. ↑ bone remodeling unit.
↓Osteoblastic function Kidney :-↑ Ca2+ reabsorption in DCT & ↑PO4 3- excretion. Intestine:-↑Ca2+ absorption through the formation of calcitriol. PTH ↓Ca2+ level in milk saliva & ocular lens
12. USES:- 1.Hypoparathyroidism:– Symptoms- low plasma Ca++ level - laryngospasm - paresthesias ,cataract PTH not used Treatment:- Acute attack:- (a) 10% calcium gluconate

- 10-20ml ,Iv. Slowly (until ceases) (b) Oral calcium salt should be started as soon as possible Chronic :- DOC . Vit-D2 Advantage:- vit-D is cheap ,effectible orally 2. Hyperparathyroidism:- ↑ PTH due to PT-tumour Symptoms:- Hypercalcemia Treatment:- surgical removal of tumour Drug:- Cinacalcet (calcimimetic agent)-orally MOA:- binds to receptor on PT gland- ↓ secretion PTH ↓ Ca++

13. Human recombinant peptide of N-terminal fragment of human PTH FDA-approved for the treatment of osteoporosis in postmenopausal woman Stimulate bone formation through its activation of osteoblast Also stimulate Intestinal absorption of dietary Ca & P Route:- SC.OD Advantage:- rapid absoption % BA-95% SE:- Transient hypercalcemia

Dizziness ,Nausea, leg cramp USES:- Treatment of severe osteoporosis

14. Hypocalcemic peptide hormone. Secreted from parafollicular cell ('C' cells)of thyroid gland Calcitonin secretion is stimulate when the serum calcium level becomes high and vice versa. Calcitonin BONE Directly inhibit osteoclasts of bone ↓ Bone resorption Kidney (-) reabsorption of Ca++ & Phosphate in renal tubule ↓ ↓Plasma Calcium ↓ ↓ plasma phosphate

15. MOA:- Acts through GPCR present on osteoclasts and inhibit their function & resorption Calcitonin preparation:- 1.Porcine calcitonin (natural) :- antigenic in nature-can lead to production of antibodies 2.Synthetic salmon calcitonin:- Synthetic form given by nasal

spray bone resorption by (-) osteoclast activity Also ↓ Ca2+ & PO4 from kidney ↑ their

Excretion Used:- Osteoporosis, hypercalcemia SE:- flushing of face & hand 3.Synthetic human calcitonin

16. 1.Hypercalcemic states 2.Post menopausal osteoporosis & corticosteroid induced osteoporosis – salmon calcitonin used as a nasal spray along with Ca and vit-D supplement

Or : Calcium 100 IU s/c or i/m daily with vit.D& calcium supplement 3. Paget's disease:- 2nd line drug

17. Vitamin-D Fat soluble vitamin Prohormone Vit-D+ PTH Central role in maintenance of plasma Ca and Bone formation Source:- Fish, liver oil ,dairy product ,also synthesize in the skin on exposure to sunlight M.O.A.:- Vit. D acts on cytoplasmic receptor Drug receptor complex translocates to nucleus Transcription of m-RNA Translation of new proteins

18. Provitamin D3 Provitamin D2 [7-dehydrocholesterol] [Ergo sterol] (skin) UV rays Vitamin D3 Vitamin D2 [Cholecalciferol] [Ergocalciferol] Liver(25-hydroxylation) Calcifediol 25-OH-D2 [25-OH-D3] [25-OH-ergocalciferol] Kidneys(1α-hydroxylation) Calcitriol 1α-25-(OH)2 ergocalciferol 1,25-dihydroxycholecalceferol (Active metabolites)

19. Human requirement & units:- Premature & normal infants 200 IU/day Adolescent & beyond 200 IU/day Pregnancy & lactation 1000 IU/day 1µg of cholecalciferol 40 IU/day Pharmacological actions:- Intestine:-↑ Absorption of calcium & phosphate Bone:- Vit.D promotes resorption & mobilization of Ca2+ from bone by promoting recruitment of osteoclast precursor cells to resorption site. 3. Kidney:-↑ proximal tubular reabsorption of both calcium & phosphorus. 4. Other effects:- Maturation & differentiation of mononuclear cells which influences cytokine production & immune function.

20. Hormone Serum Phosphate Serum Ca++ Remark Vit-D ↑ (due to ↑ intestinal absorption & ↓ renal excretion) ↑ (due to ↑intestinal absorption & ↓ renal execration Inhibits epidermal Proliferation

21. 1.Ergocalciferol (Calciferol/vit-D2) :- oral cap. Derived from yeast 2. Cholecalciferol (Vit-D3) :- 3.Calcitriol (vit-D3) active form 4.Alfacalcidol (1-α-Hydroxy cholecalciferol) 5. Calcipotriol :- Vit-D analogue used topically in psoriasis Therapeutic uses of Vit-D:-

1.Prevention (400IU/day) treatment (4000IU/day)of nutritional rickets &osteomalacia 2.Vit D resistant rickets &osteomalacia:- large dose of Vit-D + phosphate 3.Vit-D dependent rickets:- Inborn error of vit-D metabolism. there is failure of conversion of calcifediol to calcitriol.it responds to calcitriol (0.25-0.5mcg/day)or alfacalcidol

22. 4. Renal rickets:- associated with chronic renal failure. responds to calcitriol or alfacalcidol 5.Vit-D analogue,calcipotriol is used topically in the treatment of psoriasis 6.Post menopausal osteoporosis:- Vit-D + Calcium Improve calcium balance also reduce risk of fractures.

23. Analogues of pyrophosphate Bisphosphonates MOA:- they exert antiresoptive effect. Acts by inhibiting osteoclast medicated bone resorption by enhancing apoptosis of osteoclast

decrease bone resorption BISPHOSPHONATES First generation:- EtidronateClodronate Tiludronate Second generation Alendronate IbandronatePamidronate Third generation RisedronateZoledronate

24. Side effects Oral Intravenous Short term Erosive esophagitis Nausea Dyspepsia Abdominal pain Gastritis Long term Osteonecrosis of the jaw Subtrochanteric femoral fracture Severe suppression of bone turnover Hypocalcaemia Esophageal cancer Fever ,chills Headache Acute-phase reaction Muscle bone & joint pain Eye inflammation Nephrotic syndrome

25. Post menopausal osteoporosis Steroid induced osteoporosis Paget's disease Breast & prostate cancer Hypercalcemia of malignancy Recent evidence suggest that second & third generation bisphosphonate also may be effective anticancer drugs

Contraindication:- peptic ulcer Renal dysfunction Esophageal motility disorder Interaction:- Calcium suppliments,antacids,divalent cations such as Iron may interfere with intestinal absorption of bisphosphonate

26. -:Denosumab:- Fully human monoclonal antibody. Mechanism- RANKL bind to RANK leading to formation of osteoclasts cell & ↑bone resorption Decrease bone density Adverse effects:- Arthralgia, back pain,nasopharyngitis,headache,extremity pain Contraindication:- Severe hypocalcemia Impaired renal function Inhibited by Denosumab

27. Selective estrogen receptor modulators Raloxifene- only approved SERM for prevention & treatment of postmenopausal osteoporosis & vertebral fracture Mechanism- - they have estrogen receptor agonist activity in tissue