Pharmacology

Dentistry College

TIKRIT UNIVERSITY

(2024-2025)

Year 3

Assistant lecturer

FARAH MOHAMMED NAJEEB

https://www.youtube.com/watch?v=U96He401wj4

Pharmacological Principles

- Common terms used in pharmacology. (Pharmacokinetics and Pharmacodynamics).
- Safe Medication Administration.
- Individual Considerations of Medication.
- Dosage Calculation.
- Adverse Effects, Interactions, and Contraindications.

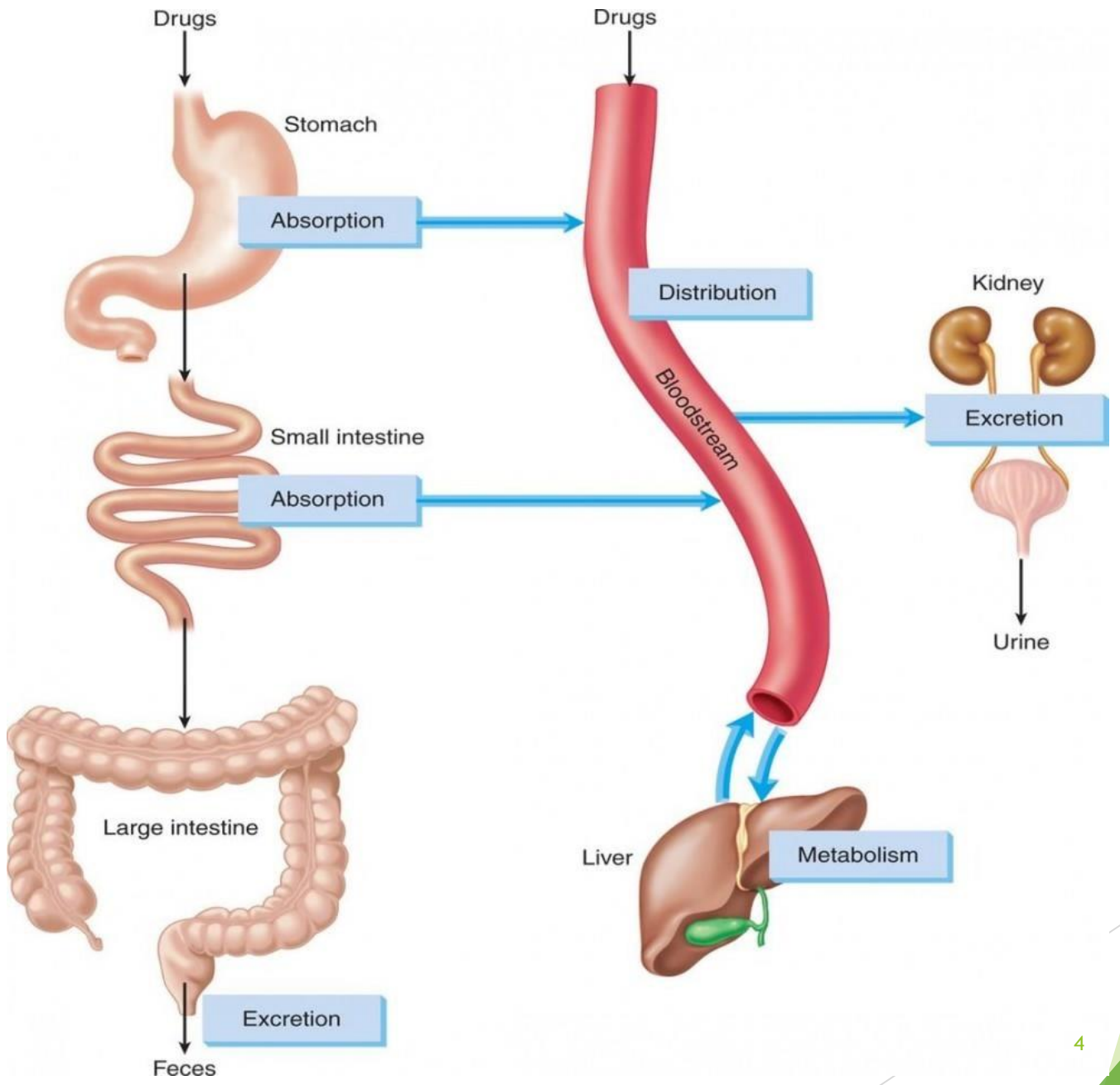
- A **drug** can be defined as a natural product, chemical substance, or pharmaceutical preparation intended for administration to a human or animal or to diagnose or treat a disease.

- Drugs may be **hormones, neurotransmitters,** or **peptides** produced by the body.

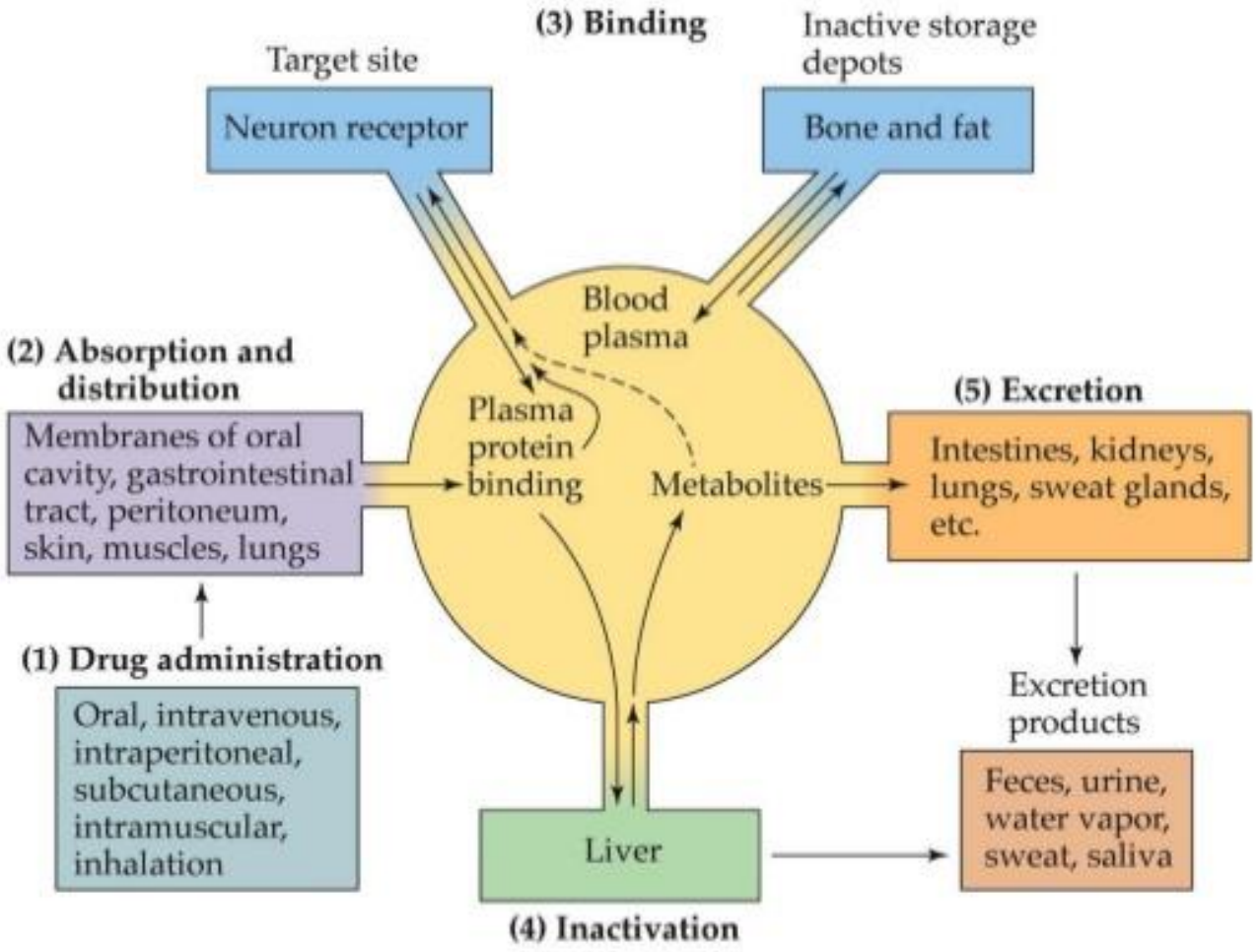
- The terms **medication** and, used less frequently, **medicament** are synonymous with the word *drug*.

Pharmacokinetics

- Pharmacokinetics is derived from two words: ***Pharmacon,*** meaning drug and ***kinesis,*** meaning movement.
- In short, it is ‘what the body **does** to the drug’. It includes **Absorption** (A), **Distribution** (D), **Metabolism** (M) and **Excretion** (E) of a drug.
- All these processes involve the movement of the drug molecule through various biological membranes.


Drugs
Stomach
Absorption
Small intestine
Absorption
Large intestine
Excretion
Feces
Drugs
Distribution
Bloodstream
Kidney
Excretion
Urine
Liver
Metabolism

Pharmacokinetics



PSYCHOPHARMACOLOGY, Figure 1.1 © 2005 Sinauer Associates, Inc.

Phases of Pharmacokinetics

Absorption is the movement of a drug from the site of administration into the bloodstream is known as absorption.

- The most common routes of administration are **enteral** (through the GI tract) and **parenteral** (by injection).
- Each of these routes will have a unique pattern of absorption.
- The medication absorption rate determines how soon the medication will take effect.
- The amount of medication absorbed determines its intensity.
- The route of administration affects the rate and amount of absorption.

Factors Influencing Drug Absorption

1. Physicochemical properties of the drug:

- **Physical state**: The liquid form of the drug is better absorbed than solid formulations.
- **Particle size:** Drugs with smaller particle sizes are absorbed better than larger ones, e.g., microfine aspirin, digoxin, griseofulvin, etc., are well absorbed from the gut and produce better effects. Some of the anthelmintics have larger particle sizes. They have poorly absorbed through the gastrointestinal (GI) tract and hence produce better effects on gut helminths.

2. **Route of drug administration:** A drug administered by intravenous route bypasses the absorption process, as it directly enters the circulation. Drugs like insulin are administered parenterally because they are degraded in the GI tract during oral administration.

3. **Food:** The presence of food in the stomach can affect the absorption of some of the drugs. Food decreases the absorption of Rifampicin, Levodopa, etc.; hence they should be taken on an empty stomach for better effect. Milk and milk products **decrease the absorption of tetracyclines**. Fatty meal **increases the absorption of griseofulvin.**

4. **Presence of other drugs:** Concurrent administration of two or more drugs may affect their absorption, e.g., ascorbic acid increases the absorption of oral iron. Antacids reduce the absorption of tetracyclines.

5. **Pharmacogenetic factors:** Genetic factors may influence drug absorption. In pernicious anaemia, vitamin B12 is not absorbed from the gut due to a lack of intrinsic factors.

6. **Area of the absorbing surface:** Normally, drugs are better absorbed in the small intestine because of a larger surface area. Resection of the gut decreases the absorption of medications due to a reduced surface area.

Bioavailability

It is the fraction of a drug that reaches the systemic circulation from a given dose. **The intravenous route** of drug administration gives 100% bioavailability, as it directly enters the circulation. The term bioavailability is commonly used for drugs given by oral route.

If two formulations of the same drug produce equal bioavailability, they are said to be bioequivalent.

If formulations differ in their bioavailability, they are said to be non-bioequivalent.

Factors Affecting Bioavailability

The factors that affect drug absorption (physicochemical properties of the drug, route of drug administration, pH and ionisation, food, presence of other medications, pharmacogenetic factors, area of absorbing surface, gastrointestinal and other diseases) also affect the bioavailability of a drug. Other factors that affect the bioavailability of a drug are discussed as follows:

1. **First-pass metabolism**

2. **Hepatic diseases:** They result in a decrease in drug metabolism, thus increasing the bioavailability of drugs that undergo first-pass metabolism, e.g., propranolol and lignocaine.

First-pass metabolism (First-pass effect, pre-systemic elimination):

When drugs are administered orally, they have to pass via the:
Gut wall Portal vein Liver Systemic circulation. During this passage, certain drugs get metabolized and are removed or inactivated before they reach the systemic circulation. This process is known as **first-pass metabolism**. The net result is decreased drug bioavailability and diminished therapeutic response. Consequences of high first-pass metabolism:

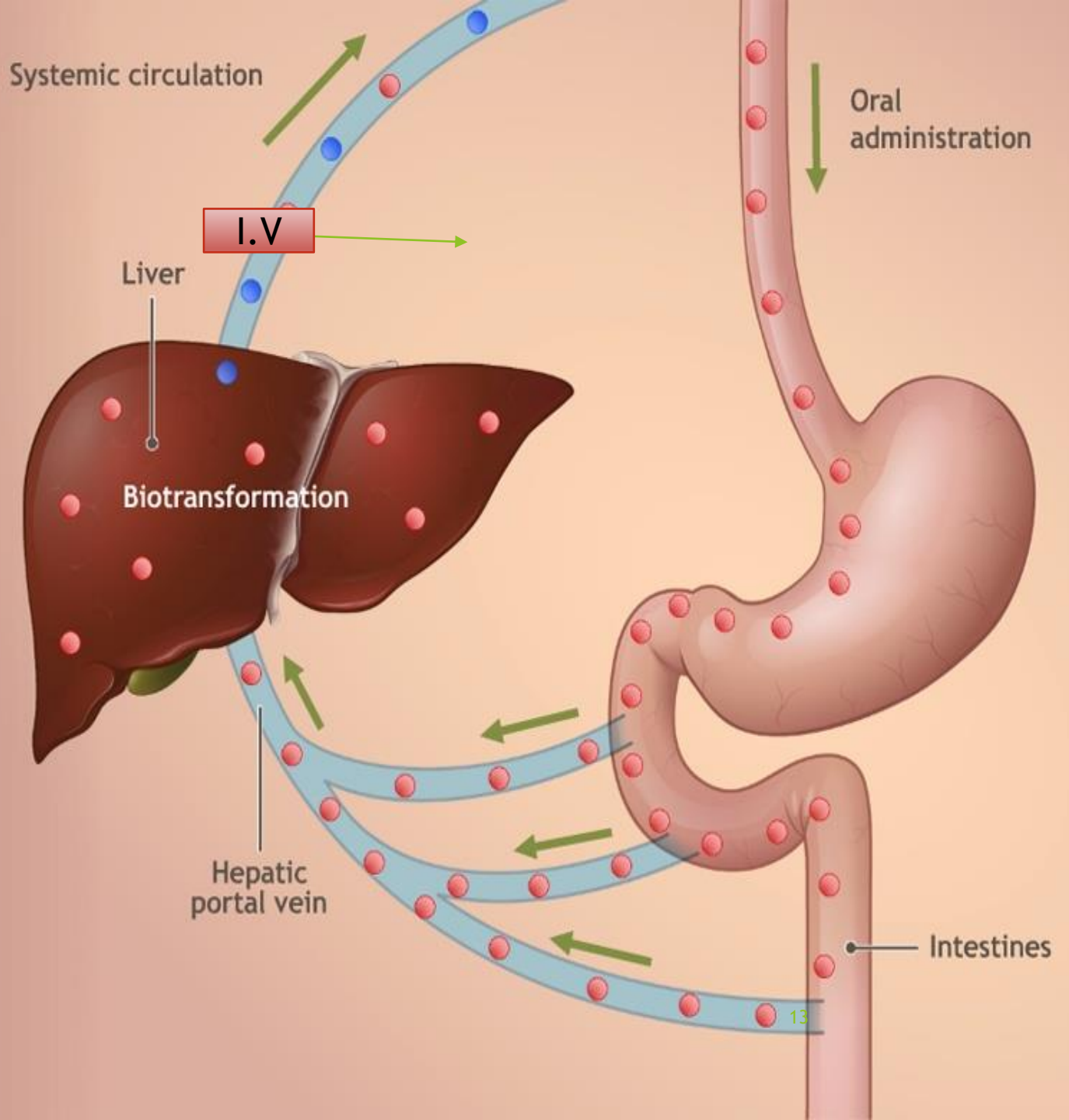
- Drugs that undergo extensive first-pass metabolism are **administered parenterally,** e.g., lignocaine is administered intravenously in ventricular arrhythmias.
- The dose of a drug required for oral administration **is more than** that given by other systemic routes, e.g. nitroglycerin.

First-Pass Metabolism

After a drug is absorbed into the gastrointestinal system, it travels through the **portal vein** into the liver, where it may be metabolized before entering circulation. Extensive metabolic elimination of a drug that greatly reduces its circulating concentration is known as first-pass metabolism. In some cases, such as with the drug **nitroglycerin**, first-pass metabolism removes all or most of the dose given before it reaches circulation. Drugs that undergo extensive first-pass metabolism can only be given in relatively high oral doses in order to be effective.

You will learn more about the metabolism of drugs in another section of this learning program.

Select the Play button to see the process of first-pass metabolism.



Distribution is defined as the reversible transfer of drugs between body fluid compartments. After absorption, a drug enters the systemic circulation and is distributed in the body fluids. In other words, **it is the transportation of medications to sites of action by bodily fluids.**

Distribution may be influenced by the following:

Drug Tissue Storage

Some drugs are concentrated or accumulated in tissues or organs of the body, which can lead to toxicity on chronic use for example, tetracyclines bones and teeth.

Plasma protein binding: Medications compete for protein binding sites within the bloodstream, primarily albumin. The ability of a medication to bind to a protein can affect how much of the medicine will leave and travel to target tissues. Two drugs can compete for the same binding sites, resulting in toxicity.

Barriers: Medications that are lipid soluble or have a transport system can cross the blood-brain barrier (BBB) or the placenta.

Clinical Importance of Plasma Protein Binding

- Drugs that are highly bound to plasma proteins have a **low volume of distribution.**
- Plasma protein binding **delays** the metabolism of drugs.
- The bound form is not available for filtration at the glomeruli; hence excretion of highly plasma-protein-bound drugs **is delayed.**
- Highly protein-bound drugs have a **longer duration** of action, e.g. Sulphadiazine is less plasma protein bound and has a duration of action of 6 h, whereas sulphadoxine is highly plasma protein bound and has a duration of action of 1 week.

- In case of poisoning, highly plasma-protein-bound drugs are difficult to be removed by **haemodialysis.**
- In diseases like anaemia, renal failure, chronic liver diseases, etc., plasma albumin levels are low. So, there will be an **increase in the free form of the drug,** which can lead to drug **toxicity.**
- Plasma protein binding can cause **displacement interactions**. More than one drug can bind to the same site on plasma protein. The drug with higher affinity will displace the one having lower affinity and may result in a sudden increase in the free concentration of the drug with lower affinity.

Metabolism (biotransformation)

The chemical alteration of the drug in a living organism is called biotransformation. The metabolism of a medication usually converts **lipid-soluble and unionised compounds into water-soluble and ionised compounds.** They are not reabsorbed in the renal tubules and are excreted.

Sites: The liver is the main site for drug metabolism; other sites are the GI tract, kidney, lungs, blood, skin and placenta.

Drug metabolism results in inactivation, but sometimes a compound with **pharmacological activity may be formed.**

Factors influencing the rate of medication metabolism include:

- **Age:** Neonates and the elderly metabolize some drugs to a lesser extent than adults. In both cases, the impairment is due to diminished activity of hepatic microsomal enzymes.
- **Diet:** Poor nutrition can decrease enzyme function.
- **Diseases:** Chronic liver diseases may affect the hepatic metabolism of some drugs, e.g., increased duration of action of diazepam in patients with cirrhosis due to impaired metabolism.
- **Genetic factors** (pharmacogenetics): These factors also influence drug metabolism. The study of genetically determined variation in drug response is called pharmacogenetics.

e.g., **Glucose-6-phosphate dehydrogenase** (G6PD) deficiency and haemolytic anaemia: G6PD activity is essential to maintain the integrity of the RBCs. A person with G6PD deficiency may develop haemolysis when exposed to certain drugs like Sulphonamides, salicylates, and dapsone.

Concurrent administration of drugs: This can result in increased or decreased metabolism of drugs (Enzyme induction or inhibition).

Enzyme Induction

Repeated administration of certain drugs increases the synthesis of microsomal enzymes. This is known as enzyme induction. The drug is an enzyme inducer, e.g., **rifampicin, phenytoin, barbiturates, carbamazepine, griseofulvin, etc.**

Clinical importance of enzyme induction

- Enzyme induction may **accelerate the metabolism** of drugs, thus **reducing the duration and intensity** of drug action, which leads to **therapeutic failure**, e.g., rifampicin and oral contraceptives. Rifampicin induces the drug-metabolizing enzyme of oral contraceptives, thus enhancing its metabolism and leading to contraceptive failure.
- Autoinduction may lead to the development of **drug tolerance**, e.g., carbamazepine, which enhances its own metabolism.
- Enzyme induction can lead to drug toxicity, e.g., increased incidence of hepatotoxicity with paracetamol in alcoholics due to the overproduction of toxic metabolite of paracetamol.

Enzyme Inhibition

Certain drugs inhibit the activity of drug-metabolizing enzymes and are known as enzyme inhibitors, e.g., **chloramphenicol, ciprofloxacin, erythromycin**, etc. Enzyme inhibition is a rapid process as compared to enzyme induction.

Clinical relevance of enzyme inhibition:

Increased incidence of bleeding with warfarin due to concomitant administration of erythromycin or chloramphenicol, etc. These drugs inhibit the drug-metabolizing enzyme of warfarin, resulting in increased plasma concentration of warfarin and enhanced anticoagulant effect (bleeding).

- **Excretion** is the elimination of medications from the body, primarily through the kidneys. Elimination also takes place through the liver, lungs, bowel, and exocrine glands. **Renal dysfunction** may lead to an increase in the duration and intensity of medication response.

Kidney: The processes involved in the excretion of drugs via the kidney are glomerular filtration, passive tubular reabsorption and active tubular secretion. Glomerular filtration and active tubular secretion facilitate drug excretion, whereas tubular reabsorption decreases drug excretion.

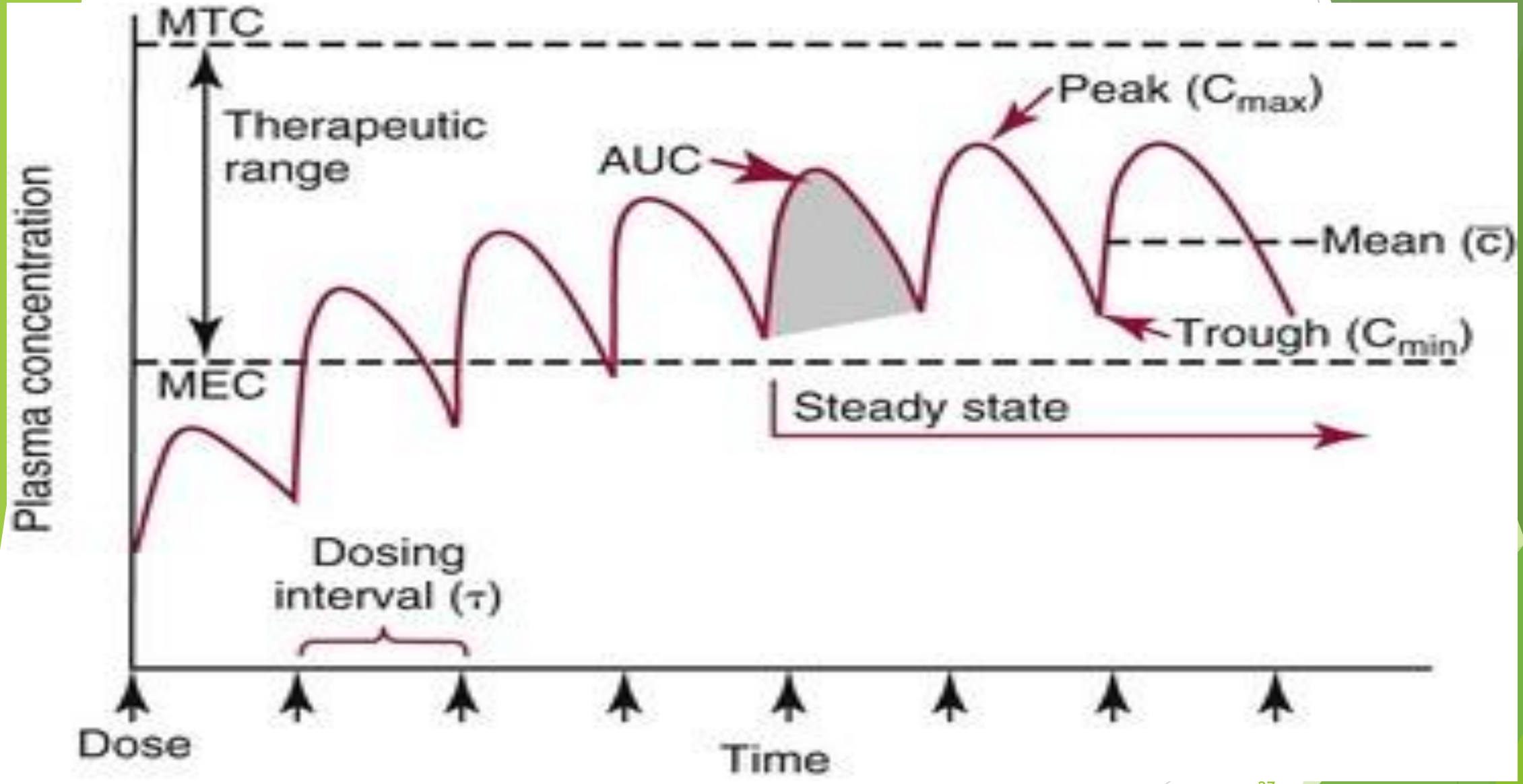
- **Lungs:** Alcohol and volatile general anaesthetics such as ether & halothane are excreted via the lungs.
- **Faeces:** Drugs that are not completely absorbed from the GI tract are excreted in faeces, e.g., senna.
- **Skin:** Metals like arsenic and mercury are excreted through the skin.
- **Saliva:** Certain drugs like potassium iodide, phenytoin, metronidazole and lithium are excreted in saliva.
- **Milk:** Drugs taken by lactating women may appear in the milk. It has acidic pH; hence essential drugs like tetracycline, chloramphenicol, morphine, diazepam, etc., remain in ionized form and are excreted through milk; hence they may affect the suckling infant.

Pharmacokinetic Parameter

- **Medication responses** – Plasma medication levels can be regulated to control medication responses. Medication dosing attempt to maintain plasma levels between the **M**inimum **E**ffective **C**oncentration (MEC) and the **T**oxic **C**oncentration (TC). A plasma medication level is in the therapeutic range when it is effective and not toxic. Therapeutic levels are well established for many medications, and these levels can be used to monitor a patient's response.

Therapeutic index (TI) – Medications with a high TI have a wide safety margin. Therefore, there is **no need for routine serum medication level monitoring**. Medications with a low TI should have serum medication levels monitored closely. Monitor peak levels based on the route of administration. For example, an oral medication may have a peak of 1 to 3 hrs after administration. If the medication is given intravenously, the peak time might occur within 10 min.

- **Half-life (t1/2)** refers to the period needed for the medication to be reduced by 50% in the body. Half-life may be affected by liver and kidney function. It usually takes four half-lives to achieve a steady state of serum concentration (medication intake = medication metabolism and excretion).
- Plasma t1/2 of lignocaine is one h and is four h for aspirin.


MTC
Therapeutic range
Peak (C_{max})
AUC
Mean ($\bar{C}$)
Trough (C_{min})
MEC
Steady state
Plasma concentration
Dosing interval (τ)
Dose
Time

By definition, the plasma concentration of a drug is halved **after one elimination half-life.** Therefore, in each succeeding half-life, less medication is eliminated. After one half-life, the amount of drug remaining in the body is 50%; after two half-lives, 25%, etc. After four half-lives, the amount of drug (6.25%) is considered negligible (small amount) regarding its therapeutic effects.

Clinical Importance of Plasma Half-life

It helps to:

- Determine the duration of drug action.
- Determine the frequency of drug administration.
- Estimate the time required to reach the steady state. At a steady state, the amount of drug administrated is equal to the amount of drug eliminated in the dosing interval. During repeated drug administration, it takes approximately four-to-five half-lives to reach a steady state. A drug is almost completely eliminated in four-to-five half-lives after a single administration.


Thank you
و السلام عليكم و رحمة الله وبركاته

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Pharmacodynamics

Pharmacodynamics (*Pharmacon:* drug; *dynamics:* power): In short, it covers all the aspects relating to ‘what the drug does to the body. It studies drugs: their mechanism of action, pharmacological actions and adverse effects.

Types of Drug Action

1. Stimulation: Some drugs increase the activity of specialised cells, e.g., adrenaline stimulates the heart increasing heart rate and force of contraction.

2. Depression: Some drugs decrease the activity of specialised cells, e.g., general anaesthetics, etc., and depress the central nervous system.

3. Irritation: Certain agents on the topical application can irritate the skin and adjacent tissues. When an agent on application to the skin relieves deep-seated pain, it is known as a counterirritant (e.g. eucalyptus oil, methyl salicylate, etc.). They are useful in sprains, joint pain, myalgia, etc.

4. Replacement: When there is a deficiency of endogenous substances, they can be replaced by drugs, e.g. insulin in diabetes mellitus, thyroxine in myxedema, etc.

5. Cytotoxic: Drugs are selectively toxic for the infecting organism/cancer cells, e.g. antibiotics/ anticancer drugs.

Mechanism of Drug Action

A- Non-receptor mediated B- Receptor-mediated

Non-receptor-mediated Mechanisms

1. **By physical action:**

Demulcent: Cough syrup produces a soothing effect in pharyngitis by coating the inflamed mucosa.

Radioactivity: Radioactive isotopes emit rays and destroy the tissues, e.g., ^{131}I in hyperthyroidism.

2. **By chemical action:**
e.g., Antacids are weak bases; hence they neutralise the acid in the stomach in peptic ulcer.

3.Through enzymes: Some drugs act either by activating or inhibiting enzyme activity. a.

Drug action via enzyme inhibition:

- Angiotensin-converting enzyme inhibitors such as captopril, enalapril, etc. Act by inhibiting angiotensin converting enzyme (ACE) and are used in treating hypertension, congestive cardiac failure, etc.

- Xanthine and hypoxanthine are oxidised to uric acid by the enzyme xanthine oxidase, which is inhibited by allopurinol. Allopurinol is used to treat chronic gout and reduce uric acid synthesis.

4. Through ion channels: Some drugs directly bind to ion channels and alter the flow of ions, e.g., local anaesthetics block sodium channels in the neuronal membrane to produce local anaesthesia.

5. Through antibody production: Vaccines produce their effect by stimulating the formation of antibodies, e.g., vaccines against tuberculosis (BCG), oral polio vaccine, etc.

6. Transporters: Some drugs produce their effect by binding to transporters. Selective serotonin reuptake inhibitors (SSRIs) bind to the 5-hydroxytryptamine (5-HT) transporter, block 5-HT reuptake into neurons, and produce an antidepressant effect.

7. Others: Anticancer drugs like cyclophosphamide produce their effect by binding to nucleic acids.

Receptor-mediated Mechanisms

Receptors are macromolecules present either on the cell surface, cytoplasm or in the nucleus with which the drug binds and interacts to produce cellular changes.

Drug–receptor complex Response

For example, adrenergic receptors, cholinergic receptors (muscarinic and nicotinic), opioid receptors, etc.

Affinity: The ability of the drug to get bound to the receptor is known as affinity.

Intrinsic activity: The ability of the drug to produce pharmacological action after combining with the receptor is known as *intrinsic activity* of the drug.

Agonist: A drug capable of producing pharmacological action after binding to the receptor is called an *agonist*. (e.g., morphine and adrenaline).

Competitive antagonist: A drug that binds to receptors but is incapable of producing pharmacological action is called an *antagonist*. (e.g., naloxone and atropine). It produces receptor blockade.

Partial agonist: A drug that binds to the receptor but produces an effect less than an agonist is called a partial agonist. (e.g., pindolol).

Inverse agonist: It has a full affinity towards the receptor but produces an effect opposite to that of an agonist. For example, benzodiazepines produce antianxiety and anticonvulsant effects by interacting with their receptors; but Carbolines act as inverse agonists at benzodiazepine receptors and produce anxiety and convulsions.

The therapeutic index (TI) is an index of drug safety.

$$TI = \frac{\text{Median lethal dose } (LD_{50}) \text{ of the drug}}{\text{Median effective dose } (ED_{50}) \text{ of the drug}}$$

It is the ratio of the median lethal dose to the median effective dose.
a. **LD50:** It is the dose of a drug that is lethal for 50% of the population.
b. **ED50:** It is the drug dose that produces the desired effect in 50% of the population.

The wider the value of the therapeutic index, the safer the drug. For example, penicillin has a high therapeutic index; digitalis, lithium, and phenytoin have a narrow therapeutic index.

Combined Effects of Drugs

A combination of two or more drugs can result in an increase or a decrease in response.

Increased response

1. **Additive effect:** The combined influence of two or more drugs equals the sum of their individual effect.

Effect of drugs A + B = Effect of drug A + Effect of drug B For example, ibuprofen and paracetamol as analgesics.

2. **Potentiation (supra-additive):** The enhancement of the action of one drug by another inactive drug is called *potentiation*.

Effect of drugs A + B > Effect of drug A + Effect of drug B For example, levodopa + carbidopa; acetylcholine + physostigmine.

Carbidopa and physostigmine inhibit the breakdown of levodopa and acetylcholine, respectively, thus enhancing their effects.

3. Synergism: When two or more drugs are administered concurrently, their combined effect is greater than that of either drug alone. For example, sulphamethoxazole + trimethoprim.

Decreased response (drug antagonism):

In antagonism, the effect of one drug is decreased or abolished in the presence of another drug.

- Chemical antagonism: The opposing action of two drugs is due to their chemical property, e.g., antacids are weak bases that neutralise gastric acid; chelating agents are complex metals and are valuable in heavy metal poisoning.

- Physiological (functional) antagonism: Here, two drugs act at different receptors or other mechanisms on the same physiological system and produce opposite effects. For example, insulin and glucagon on blood sugar, adrenaline and histamine on bronchial smooth muscle produce bronchoconstriction (via histamine receptors). In contrast, adrenaline produces bronchodilatation by acting through adrenergic receptors—hence adrenaline helps to reverse bronchospasm in anaphylactic shock.

FACTORS MODIFYING DRUG ACTION

Several factors can influence drug response. Individuals may often show quantitative variations in drug response but rarely qualitative ones.

DRUG FACTORS

1. **Route of administration:** When different routes administer a drug, it commonly exhibits quantitative variations; but sometimes it may also result in qualitative variations in response.

***Quantitative variation*:** Oral doses of the drugs are usually larger than the intravenous dose (since the i.v. route produces 100% bioavailability), e.g., the intravenous dose of morphine is 5–10 mg, whereas the oral dose is 30–60 mg for the the the the analgesic effect.

***Qualitative variation*:** The drug may produce an entirely different response when administered by different routes. For example, magnesium sulphate orally produces the purgative effect; parenterally, it causes CNS depression and locally reduces oedema in the inflamed area.

2. Presence of other drugs (potentiation, synergism and antagonism)
3. Cumulation (elimination of a drug is slower than the rate of administration)

PATIENT FACTORS

1. Age: In neonates, the metabolising function of the liver and excretory function of the kidney is not fully developed, e.g., chloramphenicol can cause grey baby syndrome.

In adults, penicillin G is given sixth hourly; but in infants, it is administered less frequently as the excretory function is not entirely developed.

In the elderly, renal and hepatic functions progressively decline. The incidence of adverse drug effects is also relatively higher, so drug doses have to be reduced accordingly, e.g., the dose of aminoglycosides in the elderly is less than the usual adult dose.

2. Body weight and body surface: An average dose of a drug is calculated in terms of body weight (mg/kg).

In obese, skinny and a patient with dehydration or oedema, dose calculation based on body weight is not very appropriate. A more accurate method for calculating a dose is based on the patient's body surface area (BSA). Nomograms are available to calculate BSA from the height and weight of the patient. Since it is inconvenient to calculate BSA, routinely dose is calculated on a body weight basis. The dose of anticancer drugs and a few other medicines are calculated based on BSA.

3. Sex: Drugs like Beta-blockers, diuretics and clonidine can cause decreased libido in males.

4. Diet and environmental factors: Milk reduces the absorption of tetracyclines; fatty meal increases the absorption of griseofulvin (antifungal agent).

5. Genetic factor.

6. Psychological factor: The personality of the doctor and the patient can affect the response to a drug. Some patients even respond to inert dosage forms (placebo) in conditions like pain, bronchial asthma, anxiety, etc.

Placebo effect:

'*Placebo*' is a Latin term that means "I will please". It is a dummy medicine having no pharmacological activity. The effect produced by a placebo is called the placebo effect. Sugar tablets and distilled water injections are used as placebos.

Uses

- Placebos relieve subjective symptoms like anxiety, headache, tremors, pain, insomnia, etc.
- Placebos are used in clinical trials to minimize bias.

•***Factors affecting the placebo effect are:***

- *Patient factor*: Patients with neurotic symptoms often respond to placebos.
- *Drug factor*: The placebo response can be affected by the drug's physical presentation or route of administration. For example, colourful tablets such as red, blue, and green are injectable preparations that give a better placebo effect.
- *Doctor factor*: The doctor's personality, motivation, way of instruction, doctor-patient relationship, etc., are important factors that also affect the placebo response.

7. Pathological states:

GI disorders: In malabsorption syndrome, the absorption of some drugs is reduced.

Liver disease: In chronic liver diseases, the metabolism of drugs is significantly reduced. This will increase the bioavailability of drugs having high first-pass metabolism, e.g., propranolol.

Renal failure: Clearance of drugs excreted through the kidney is impaired. For example, the incidence of nephrotoxicity and ototoxicity is more with aminoglycosides in the presence of renal failure.

8. Tolerance: Repeated administration of certain drugs can result in a decrease in their pharmacological effect. Hence, higher doses of such drugs are needed to produce a given response, e.g., ephedrine, organic nitrates, opioids, etc. Tolerance develops to the nasal decongestant effect of ephedrine on repeated use. Patients on organic nitrates for angina develop tolerance on long-term therapy. Tolerance is commonly seen with drugs like morphine, alcohol, amphetamine, etc.

DRUG INTERACTIONS

When two or more drugs are administered simultaneously, the effects of one drug may be altered by the other drug.

Drug interactions can occur either *in vitro* (outside the body) or *in vivo* (inside the body). Drug interactions can result in either beneficial or harmful effects.

Pharmaceutical Interactions

These can occur due to a drug's incompatibility (physical or chemical) with an intravenous solution or when two or more drugs are mixed in the same syringe/i.v. infusion. This may result in the precipitation or inactivation of one or more drugs.

Pharmacokinetic Interactions

These occur when one drug alters another drug's absorption, distribution, metabolism or excretion.

Absorption: Antacids (containing aluminium, magnesium, calcium, iron, etc.) interfere with the absorption of tetracyclines by forming unabsorbable complexes.

Distribution: Plasma protein binding can cause displacement interactions. More than one drug can bind to the same site on plasma protein.

Metabolism: This occurs when the metabolism of one drug is increased (enzyme induction) or decreased (enzyme inhibition) by another drug.

Excretion: Most of them occur in the kidneys. Salicylates interfere with the excretion of methotrexate and potentiate its toxicity. Probenecid decreases the renal tubular secretion of penicillins and prolongs the duration of action of penicillins (beneficial interaction).

Pharmacodynamic Interactions

The interaction is due to the action of drugs on receptors or the physiological system. This may result in either additive, synergistic or antagonistic effects. The interactions may also result in harmful effects, e.g., enhanced nephrotoxicity seen with the concurrent use of aminoglycosides and amphotericin B; it may also result in beneficial effects, e.g., levodopa and carbidopa in parkinsonism.

ADVERSE DRUG REACTIONS

The adverse effect is any undesirable or unwanted effect due to drug administration. The WHO suggested definition of adverse drug reactions (ADR) and adverse effects (AE) are as follows:

Adverse drug reaction (ADR): Any response that is noxious, unintended and which occurs at doses typically used in humans for prophylaxis, diagnosis or disease therapy, or modification of physiological function (WHO).

Adverse event (AE): Any untoward medical occurrence that may present during treatment with a pharmaceutical product but does not necessarily have a causal relationship with this treatment (WHO).

Predictable reactions (Type A or Augmented reactions): These are predictable reactions to a drug-related to its pharmacological actions. They include side effects, secondary effects and toxic effects.

Unpredictable reactions (Type B or Bizarre or strange reactions): These are non-dose-related unpredictable reactions to a drug. They are not related to the pharmacological actions of the drug. Allergic reactions and idiosyncrasies are unexpected reactions.

Adverse drug effects include the following:

Side Effects

These are the unwanted pharmacological effects of a drug that are seen with therapeutic doses, e.g., atropine used in the treatment of heart block also produces dryness of mouth, blurring of vision, urinary retention, etc., which are the side effects.

Secondary Effects

The primary action of a drug may result in other effects, e.g., immunosuppression by corticosteroids can lead to the development of opportunistic infections, e.g., oral candidiasis.

Toxic Effects

These drug effects are either due to overdosage or chronic use, e.g., bleeding due to chronic use/overdosage of anticoagulants and nephrotoxicity with aminoglycosides, especially in patients with renal failure.

Drug Allergy

It is an abnormal response (local or systemic) to a drug/foreign antigen mediated by the immune system. Different types of hypersensitivity reactions are discussed below.

Those associated with humoral antibodies: *Types I, II and III*. Those associated with cell-mediated immunity: *Type IV* (delayed hypersensitivity).

Type I hypersensitivity (immediate type, anaphylactic shock): It is a rapidly occurring reaction; hence they are called an immediate hypersensitivity reaction. The manifestations are itching, urticaria, hay fever, asthma, or anaphylactic shock.

Idiosyncrasy (Idiosyncrasy)

It is usually a genetically determined abnormal drug reaction, e.g., succinylcholine apnoea, aplastic anaemia caused by chloramphenicol, and haemolytic anaemia seen with primaquine and sulphonamides.

Drug Dependence

Psychological dependence: There is an intense desire to continue taking the drug as the patients feel that their well-being depends upon it.

Physical dependence: Repeated drug use produces physiological changes in the body that makes the continuous presence of the drug in the body necessary to maintain normal function. Abrupt stoppage of the drug results in an imbalance wherein the body has to readjust to the absence of the drug resulting in the development of signs and symptoms known as *withdrawal syndrome*. The withdrawal signs and symptoms are generally opposite to the effects produced by the drug.

Iatrogenic (ī¦atrəˈjenik)**Diseases**

It is a physician-induced disease (***'Iatros'*** is a Greek word means 'physician') due to drug therapy, e.g., parkinsonism due to metoclopramide, acute gastritis and peptic ulcer due to nonsteroidal anti-inflammatory drugs.

Teratogenicity

When given during pregnancy, certain drugs may cross the placenta and cause various dangerous effects on the foetus. This is called teratogenesis.

Administration of drugs during *early pregnancy* (from conception to 16 days) could result in abortion; during *2–8 weeks* of gestation, it can affect organogenesis and produce structural abnormalities; during the *second and third trimesters*, drugs can affect growth and development of the foetus. Hence, drug administration during pregnancy should be restricted.

Carcinogenicity and Mutagenicity

The ability of a drug to cause cancer is *carcinogenicity,* and the agent is known as a *carcinogen*. The abnormalities of genetic material in a cell produced by a drug are known as *mutagenicity*, e.g., anticancer drugs.

Photosensitivity Reactions

It is a drug-induced cutaneous reaction following exposure to ultraviolet radiation, e.g., demeclocycline, doxycycline, etc.

Hepatotoxicity

Some hepatotoxic drugs are isoniazid, rifampicin, pyrazinamide, halothane, paracetamol, etc.

Nephrotoxicity

Aminoglycosides, amphotericin B, cisplatin, cyclosporine, heavy metals, etc., are nephrotoxic drugs.

Ototoxicity

It can occur with aminoglycosides, loop diuretics, cisplatin, etc.

Ocular Toxicity

Ethambutol, chloroquine, glucocorticoids, etc., can cause ocular toxicity.

Pharmacovigilance

It is the science and activities relating to detecting, assessing, understanding and preventing adverse effects or other possible drug-related problems (WHO). Pharmacovigilance aims to improve patient care and safety associated with the use of drugs, promote the rational use of medicines, develop regulations for drug use, and educate healthcare professionals about adverse drug reactions.

Pregnancy safety categories

Category = Description

Category A= studies indicate **no risk** to the human fetus.

Category B = studies indicate **no risk** to animal fetuses, information on humans **is unavailable**.

Category C = adverse effects **reported** in animal fetuses, information in humans **is unavailable**.

Category D = possible **fetal risk in humans** reported, however, considering potential benefit vs. risk.

Category X = **fetal abnormalities** reported and positive evidence of fetal risk in humans is available from animal and/ or human studies. These drugs should not be used in pregnant women.


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Pharmacology

Dentistry College

TIKRIT UNIVERSITY

(2024-2025)

Year 3

Assistant lecturer

FARAH MOHAMMED NAJEEB

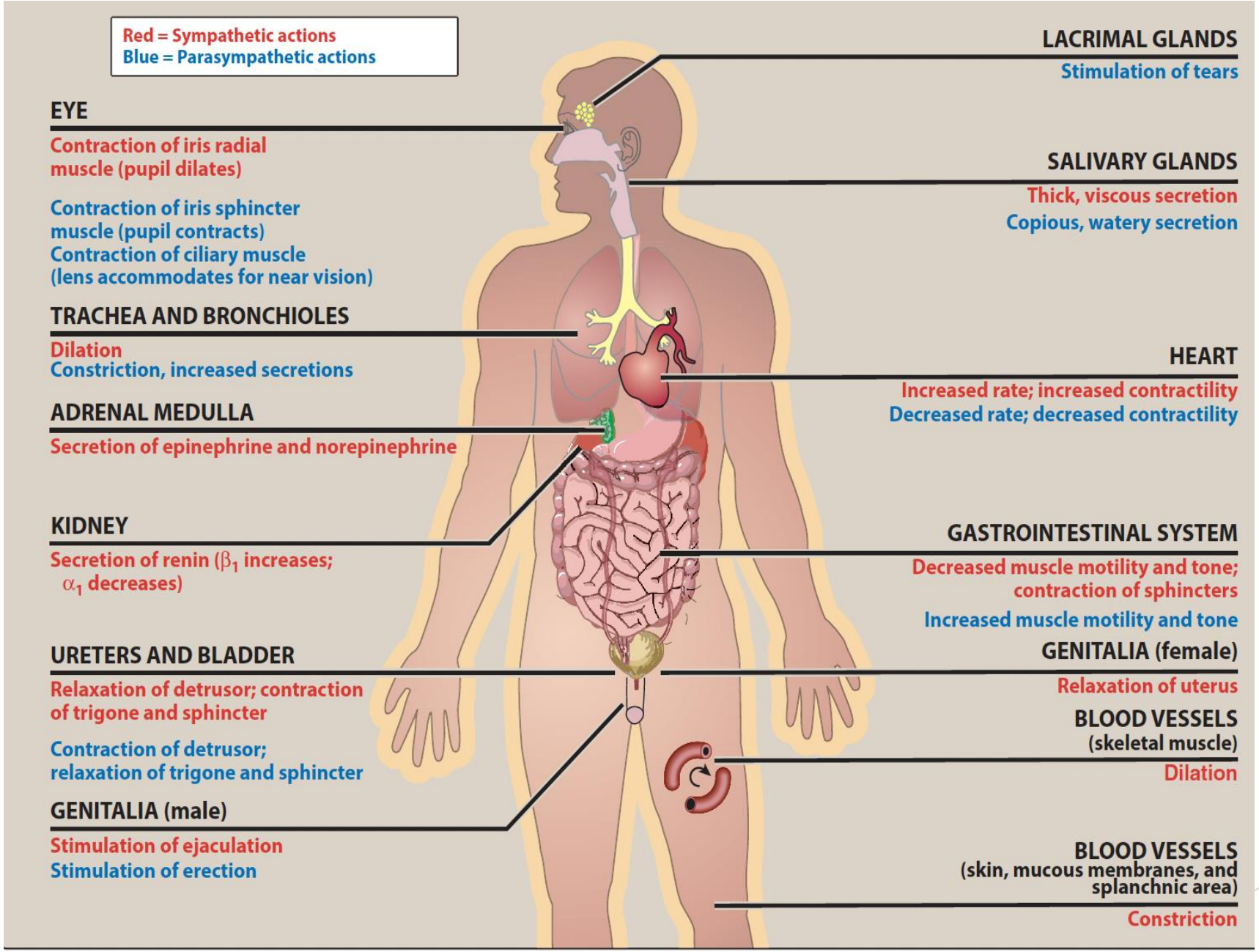


Figure 3.3
Actions of sympathetic and parasympathetic nervous systems on effector organs.

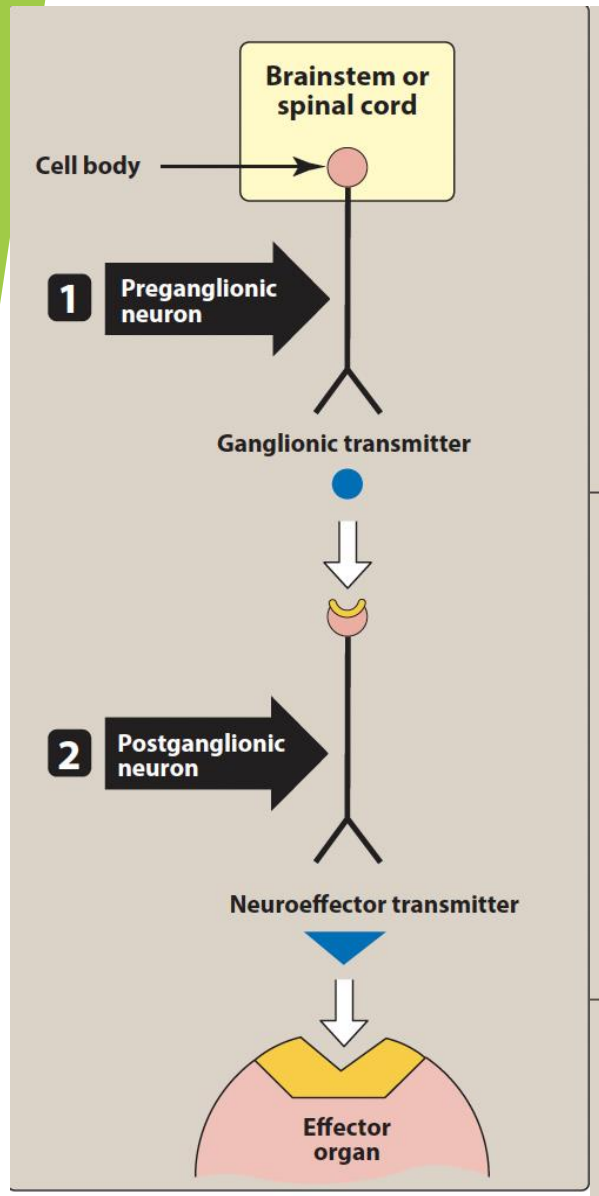


Figure 3.2
Efferent neurons of the autonomic nervous system.

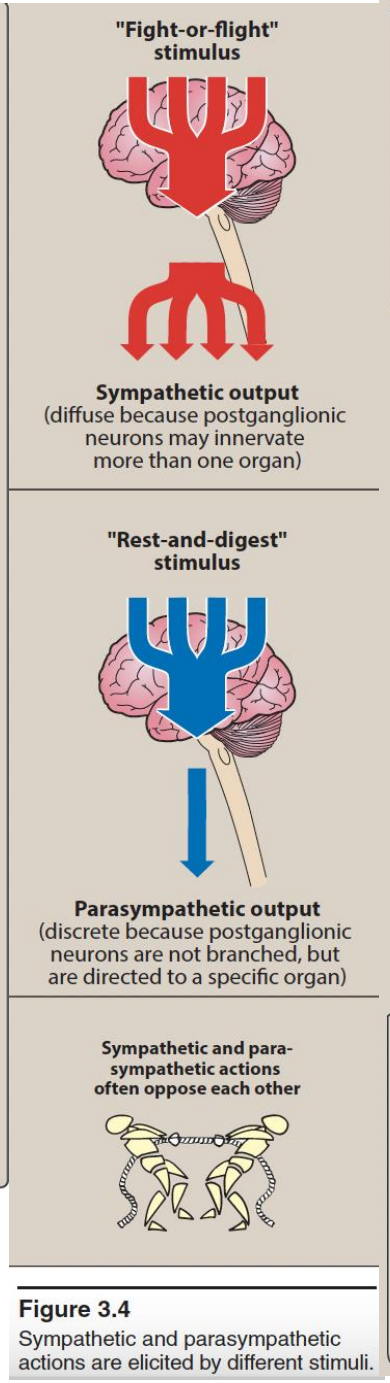
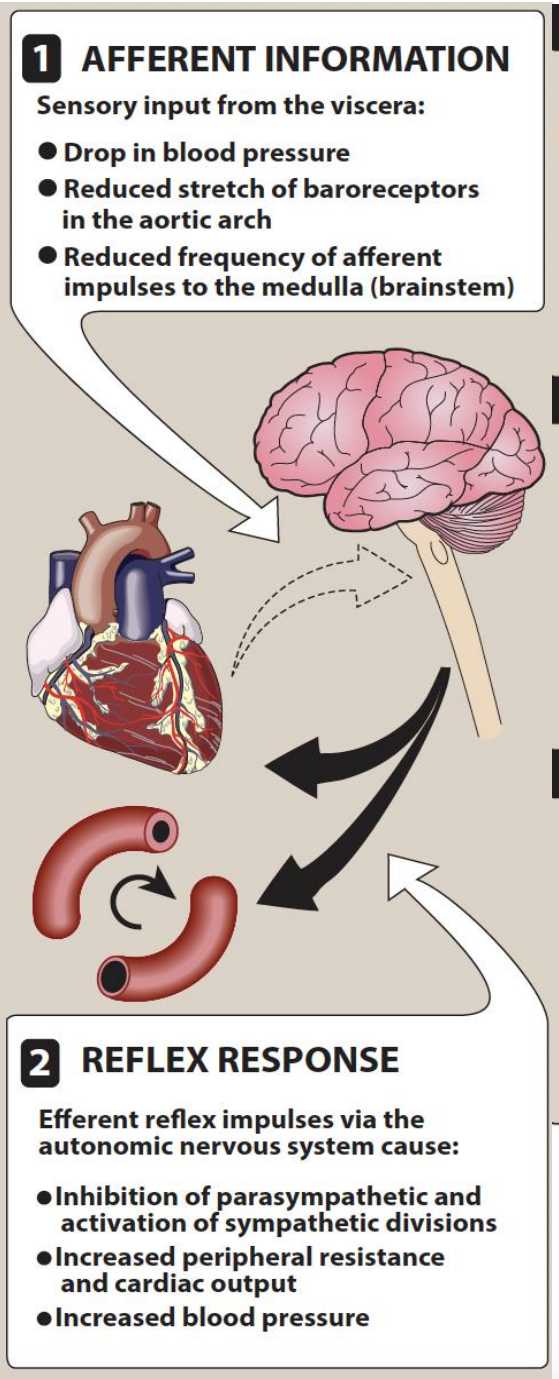


Figure 3.4
Sympathetic and parasympathetic actions are elicited by different stimuli.



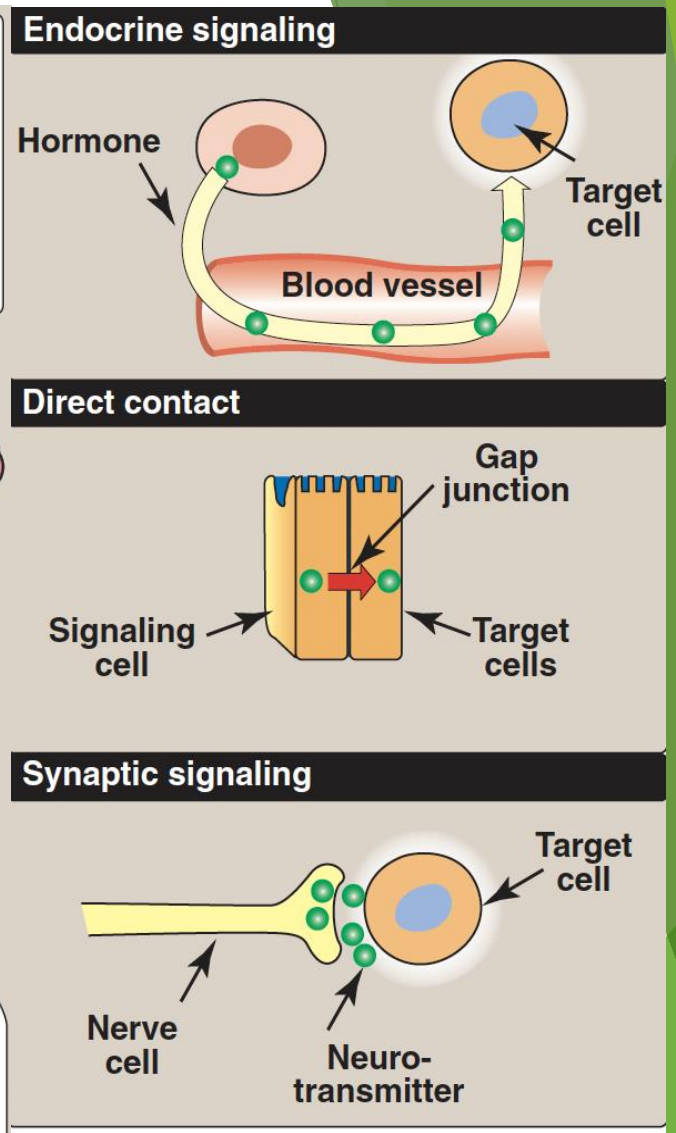
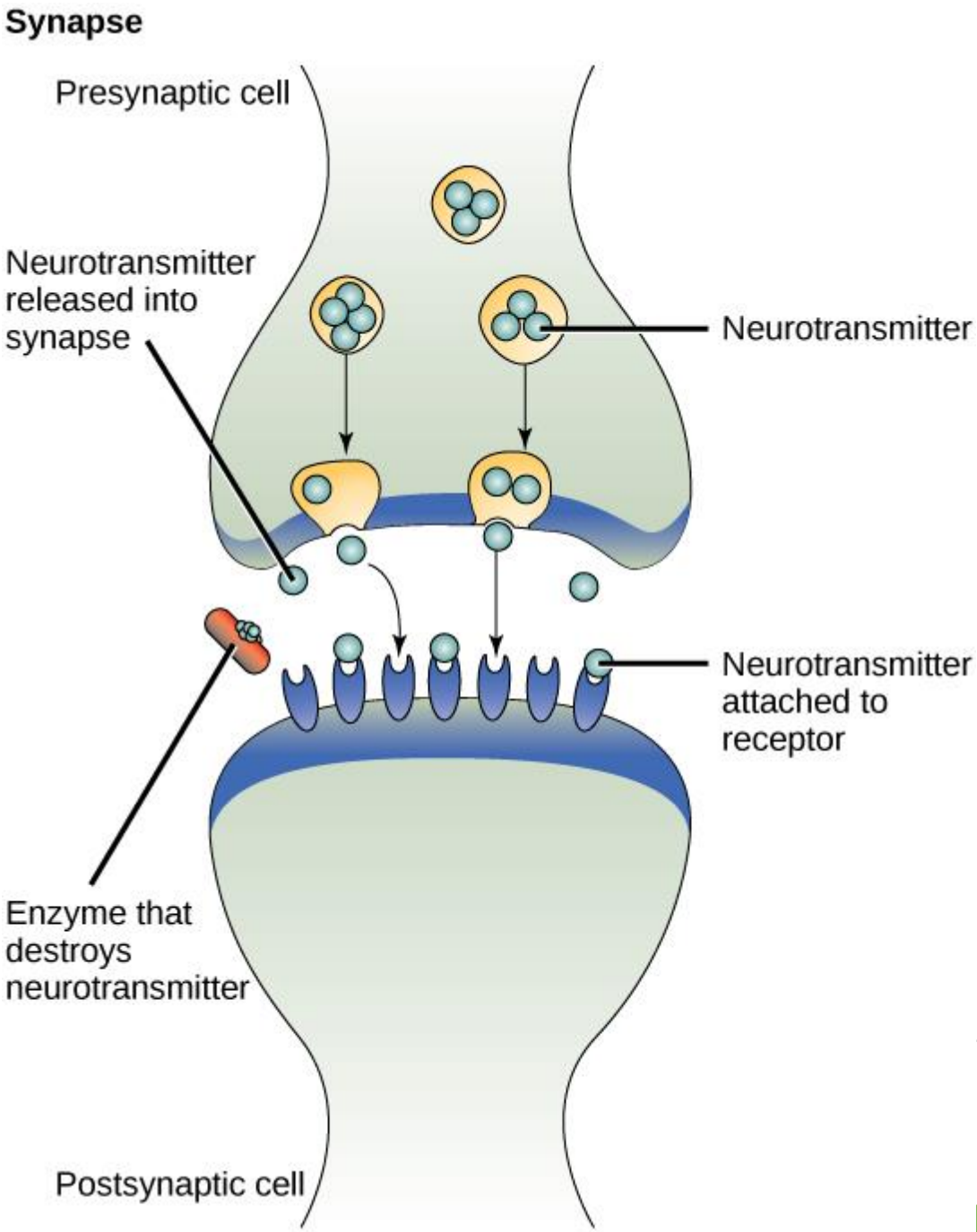


Figure 3.7
Some commonly used mechanisms for transmission of regulatory signals between cells.


Synapse
Presynaptic cell
Neurotransmitter released into synapse
Neurotransmitter
Neurotransmitter attached to receptor
Enzyme that destroys neurotransmitter
Postsynaptic cell

The Autonomic Nervous System

- The autonomic nervous system (ANS) and the endocrine system coordinate **the regulation and integration of bodily functions**.
- The endocrine system sends signals to target tissues by varying the levels **of blood-borne hormones**.
- In contrast, the nervous system exerts its influence by rapidly transmitting **electrical impulses** over nerve fibers that terminate at effector cells, which specifically respond to the release of neuro mediators substances.
- Drugs that produce their primary therapeutic effect by mimicking or altering the functions of the ANS are called **autonomic drugs.**
- These autonomic agents act either by **stimulating** portions of the ANS or **blocking the action of the autonomic nerves**.

Introduction To The Nervous System

- The nervous system is divided into two anatomical divisions:
- The **central nervous system** (CNS) is composed of the **brain and spinal cord**, and the **peripheral nervous system** includes **neurons outside the brain and spinal cord,** that is, any nerves that enter or leave the CNS.
- The peripheral nervous system is subdivided into **efferent and afferent divisions.**
- The **efferent neurons** carry signals from the **brain and spinal cord to the peripheral tissues** and the **afferent** neurons bring information from the **periphery** to the CNS.
- The afferent neurons provide sensory input to modulate the function of the efferent division through reflex arcs or neural pathways that mediate a reflex action.

Functional divisions within the nervous system

- The efferent portion of the peripheral nervous system is further divided into two major functional subdivisions: **the somatic and the ANS.**
- The **somatic efferent** neurons are involved in the **voluntary control** of functions such as the contraction of the skeletal muscles essential for locomotion.
- **The ANS, conversely**, regulates the everyday requirements of **vital bodily functions without the conscious participation of the mind**.
- Because of the involuntary nature of the ANS as well as its functions, it is also known as the **visceral, vegetative, or involuntary nervous system.**
- It is composed of efferent neurons that innervate smooth muscle of the viscera, cardiac muscle, vasculature, and exocrine glands, thereby controlling digestion, cardiac output, blood flow, and glandular secretions.

1. Effects of stimulation of the sympathetic division:

- The effect of sympathetic output is to **increase heart rate** and blood pressure, **mobilise body energy stores**, and **increase blood** flow to skeletal muscles and the heart while diverting flow from the skin and internal organs.
- Sympathetic stimulation results in the **dilation of the pupils and the bronchioles**
- It also affects **GI motility and the function of the bladder and sexual organs.**

2. Fight-or-flight response: The changes experienced by the body during **emergencies** are referred to as the “fight or flight” response. These reactions are triggered by direct sympathetic activation of the effector organs and by stimulating the adrenal medulla **to release epinephrine and lesser amounts of norepinephrine.**

Functions of the parasympathetic nervous system

- The parasympathetic division is involved with **maintaining homeostasis within the body**.
- It is required for life since it maintains essential bodily functions, such as **digestion and elimination of wastes.**
- The **parasympathetic** division usually **opposes or balances** the **sympathetic** division's actions and generally predominates the sympathetic system in "rest-and-digest" situations.
- **Parasympathetic** fibers innervating specific organs such as the **gut, heart, or eye** are activated separately, and the system functions to affect these organs individually.

Summary of differences between sympathetic, **parasympathetic, and motor nerves**

- The **sympathetic** nervous system is widely distributed, innervating practically **all effector systems in the body.**
- In contrast, the distribution of the **parasympathetic** division is **more limited**.
- **The somatic nervous system innervates skeletal muscles**. One somatic motor neuron axon is highly branched, and each branch innervates a single muscle fiber. Thus, one somatic motor neuron may innervate 100 muscle fibers. This arrangement leads to the formation of a motor unit. The lack of ganglia and the myelination of the motor nerves enable a fast response by the somatic nervous system.

Chemical Signaling Between Cell

Hormones: Specialized endocrine cells secrete hormones into the bloodstream, where they **travel** throughout the body, exerting effects on broadly distributed target cells. **Local mediators:** Most cells in the body secrete chemicals that **act locally** on cells in the immediate environment. Because these chemical signals are rapidly destroyed or removed, they do not enter the blood and are not distributed throughout the body. **Histamine and prostaglandins are examples of local mediators**. **Neurotransmitters:** Communication between nerve cells and nerve cells and effector organs occurs through the release of specific chemical signals (neurotransmitters) from the nerve terminals. The neurotransmitters rapidly diffuse across the synaptic cleft, or space (synapse), between neurons and combine with specific receptors on the postsynaptic (target) cell.

Types of neurotransmitters

Acetylcholine:

- If the transmission is mediated by acetylcholine, the neuron is termed cholinergic.
- Acetylcholine mediates the transmission of nerve impulses across autonomic ganglia in both the **sympathetic and parasympathetic** nervous systems.
- In the somatic nervous system, transmission at the neuromuscular junction (the junction of nerve fibers and voluntary muscles) is also **cholinergic**.

Norepinephrine and epinephrine:

- When norepinephrine and epinephrine are the neurotransmitters, the fiber is termed **adrenergic**. In the sympathetic system, norepinephrine mediates the transmission of nerve impulses from autonomic postganglionic nerves to effector organs. [**Note**: **A few sympathetic fibers, such as those involved in sweating, are cholinergic.**

Cholinergic Agonists

The cholinergic drugs act on receptors activated by acetylcholine (ACh), whereas the adrenergic drugs act on receptors stimulated by norepinephrine or epinephrine. Cholinergic and adrenergic drugs work by stimulating or blocking the ANS's receptors.

Direct Acting: Acetylcholine, Bethanechol, Carbachol, Pilocarpine.

Indirect Acting (Reversible): Donepezil, Neostigmine, Physostigmine, Pyridostigmine, Rivastigmine.

Indirect Acting (Irreversible): Echothiophate.

Reactivation Of Acetylcholinesterase: Pralidoxime

Cholinergic agonists mimic the effects of ACh by binding directly to cholinoceptors (muscarinic or nicotinic). All direct-acting cholinergic drugs have a **longer duration of action** than ACh. The more therapeutically beneficial drugs (**pilocarpine and bethanechol**).

A. Acetylcholine (ACh): Its actions include:

1- **Decrease in heart rate and cardiac output**. For example, if injected intravenously, ACh produces a brief decrease in cardiac rate (negative chronotropic).

2- **Decrease in blood pressure**: Injection of ACh causes vasodilation and lowers blood pressure.

3- Acetylcholine **increases salivary secretion in the gastrointestinal (GI) tract and stimulates intestinal secretions and motility.**

B. Bethanechol: Its significant actions are on the **smooth musculature** of the bladder and GI tract.

1. Actions: Increased intestinal motility. It also stimulates the detrusor muscle of the bladder and produces urination.
2. Therapeutic applications: In urologic treatment, bethanechol stimulates the atonic bladder, particularly in postpartum or postoperative, nonobstructive urinary retention.
3. Adverse effects: Sweating, salivation, flushing, decreased blood pressure, nausea, abdominal pain, diarrhoea, and bronchospasm. **Atropine** sulfate may be administered **to overcome** this agent's severe cardiovascular or bronchoconstrictor responses.

C. Carbachol

1. Actions: Carbachol profoundly affects the **cardiovascular and GI systems**. It can cause the release of epinephrine from the adrenal medulla by its nicotinic action. Locally instilled into the eye, causing **miosis**
2. Therapeutic uses: Because of its high potency, receptor non-selectivity, and relatively long duration of action, carbachol is rarely used therapeutically except in the eye as a **miotic agent to treat glaucoma by causing pupillary contraction and a decrease in intraocular pressure.**

3. Adverse effects: At doses used ophthalmologically, **little or no side effects** occur due to **lack of systemic penetration.**

D. Pilocarpine

1. Actions: Pilocarpine produces **rapid miosis** and contraction of the ciliary muscle. The drug **promotes salivation** in patients with **xerostomia**.
2. Therapeutic use: Pilocarpine is used to treat glaucoma and is the drug of choice for **emergency lowering of intraocular pressure of both open-angle and angle-closure glaucoma**. [Note: Topical carbonic anhydrase inhibitors, such as dorzolamide and β-adrenergic blockers, such as timolol, are effective in treating glaucoma but are not used for emergency lowering of intraocular pressure.] The miotic action of pilocarpine is also useful in **reversing mydriasis due to atropine**.

3. Adverse effects: Pilocarpine can cause blurred vision, night blindness, and brow ache.

Indirect-acting Cholinergic Agonists: Anticholinesterase Agents (Reversible)

AChE is an enzyme that cleaves ACh explicitly to acetate and choline and, thus, terminates its actions. **Inhibitors** of AChE indirectly provide a cholinergic activity by preventing the **degradation** of ACh. This results in an accumulation of ACh in the synaptic space.

A. Edrophonium: It is used to diagnose **myasthenia gravis (HOW)**. Intravenous injection of edrophonium leads to a rapid increase in muscle strength. Care must be taken because excess drugs may provoke a **cholinergic crisis** (atropine is the antidote). **Edrophonium may also assess cholinesterase inhibitor therapy, differentiate cholinergic and myasthenic crises, and reverse the effects of non-depolarising neuromuscular blockers after surgery.**

B. Physostigmine

1- Actions: Physostigmine has a wide range of effects as a result of its action and stimulates not only the **muscarinic and nicotinic** sites of the ANS but also the nicotinic receptors of the neuromuscular junction (NMJ). It is considered an intermediate-acting agent. Physostigmine **can enter and stimulate the cholinergic sites in the CNS.**

2. Therapeutic uses: The drug **increases intestinal and bladder motility**. Physostigmine is also used to treat **overdoses of drugs** with anticholinergic actions, such as **atropine.**

3. Adverse effects: **Convulsions** when high doses are used. **Bradycardia** and a fall in cardiac output may also occur.

C. Neostigmine

1. Actions: It is **absorbed poorly** from the GI tract and **does not enter the CNS**.
2. Therapeutic uses: **It stimulates the bladder and GI tract and is an antidote for competitive neuromuscular-blocking agents**. Neostigmine is also used to manage symptoms of **myasthenia gravis.**
3. Adverse effects: Generalized cholinergic **stimulation**, such as **salivation, flushing, decreased blood pressure, nausea, abdominal pain, diarrhoea, and bronchospasm**. Neostigmine **does not cause CNS side effects** and is not used to overcome the toxicity of central-acting antimuscarinic agents such as atropine. Neostigmine is contraindicated when intestinal or urinary bladder **obstruction** is present.

D. Pyridostigmine is used in the chronic management of **myasthenia gravis.** The adverse effects of these agents are similar to those of neostigmine.

E. Donepezil and Rivastigmine

Patients with **Alzheimer's disease** have a deficiency of **cholinergic neurons in the CNS**.

Despite the ability of donepezil & rivastigmine to delay the progression of Alzheimer's disease, **none can stop** its progression. **GI distress is their primary adverse effect.**

Indirect-acting Cholinergic Agonists: Anticholinesterase Agents (Irreversible)

Many of these drugs are **highly toxic** and were developed by the military as nerve agents. Related compounds, such as **parathion and malathion**, are used as insecticides.

A. Echothiophate:

1. Actions include generalized cholinergic stimulation, paralysis of motor function (causing **breathing difficulties**), and **convulsions**. Echothiophate produces **intense miosis** and, thus, has found therapeutic use. Intraocular pressure falls from the facilitation of the outflow of aqueous humour. **Atropine** in high dosages can reverse many of the peripheral and some of the central muscarinic effects of echothiophate.
2. Therapeutic uses: A topical ophthalmic solution of the drug is available to treat open-angle glaucoma.
3. Echothiophate is rarely used due to its side effect profile, which includes the risk of causing **cataracts**.

Toxicology of Anticholinesterase Agents

Irreversible AChE inhibitors (mostly organophosphate compounds) are commonly used as agricultural insecticides, which has led to numerous cases of accidental poisoning with these agents. In addition, they are frequently used for suicidal and homicidal purposes. Organophosphate nerve gases such as sarin are used as warfare agents and chemical terrorism.

A. Reactivation of acetylcholinesterase

Pralidoxime (2-PAM) can reactivate inhibited AChE. Pralidoxime is a weak AChE inhibitor and, at higher doses, may cause side effects like other AChE inhibitors.

B. Other treatments: Atropine is administered to prevent the muscarinic side effects of these agents. Such effects include increased bronchial and salivary secretion, bronchoconstriction, and bradycardia. **Diazepam** is also administered to reduce the persistent convulsion caused by these agents.

Cholinergic Antagonists

The most clinically useful of these agents are selective blockers of muscarinic receptors. They are commonly known as anticholinergic agents.

Antimuscarinic Agents: Atropine, Benztropine, **Cyclopentolate**, **Ipratropium**, **Oxybutynin**, **Scopolamine**, **Tolterodine**, **Trihexyphenidyl**, **Tropicamide.**

Ganglionic Blockers: Nicotine

Neuromuscular Blockers: Succinylcholine

Antimuscarinic Agents (anticholinergic)

Anticholinergic drugs are beneficial in a variety of clinical situations. [**Note: Several antihistamines and antidepressants (mainly tricyclic antidepressants) also have antimuscarinic activity**.]

A. Atropine: Atropine acts both **centrally and peripherally**. The greatest inhibitory effects are on **bronchial tissue and the secretion of sweat and saliva.**

1. Actions:

a. Eye: Mydriasis (pupil dilation), unresponsiveness to light, and cycloplegia (inability to focus for near vision). In patients with angle-closure glaucoma, **intraocular pressure may rise dangerously.**

b. Gastrointestinal (GI): Atropine can be used as an **antispasmodic** to reduce the activity of the GI tract. Atropine and scopolamine are probably the **most potent antispasmodic** drugs available. Atropine is **NOT** effective for the treatment of **peptic ulcers**.

c. Cardiovascular: (**Divergent effect**) **At low doses**, the predominant effect is a **slight decrease in heart rate (M1 Receptor)**. **Higher doses of atropine** cause a progressive **increase in heart rate (M2 Receptor).**

d. Secretions: Producing mouth dryness (xerostomia). [Note: Inhibition of secretions by sweat glands can cause elevated body temperature, which can be dangerous in children and the elderly.]

2. Therapeutic uses:

a. Ophthalmic: Topical atropine exerts both **mydriatic and cycloplegic** effects. Shorter-acting antimuscarinics (cyclopentolate and tropicamide) have replaced mainly atropine due to prolonged mydriasis observed with atropine.

b. Antispasmodic: Atropine is used as an antispasmodic agent to relax the GI tract.

c. Cardiovascular: The drug is used to treat **bradycardia** of varying **etiologies.**

d. Antisecretory: Atropine is sometimes used as an antisecretory agent **to block secretions** in the upper and lower respiratory tracts **before surgery**.

e. **Antidote** for cholinergic agonists: Atropine is used to treat organophosphate (insecticides, nerve gases) poisoning. The ability of atropine to **enter the central nervous system (CNS)** is of particular importance in treating the central toxic effects of anticholinesterases.

3. Adverse effects: **Depending on the dose, atropine may cause dry mouth, blurred vision, "sandy eyes - Gritty eyes," tachycardia, urinary retention, and constipation**.

Effects on the CNS include **restlessness, confusion, hallucinations, and delirium, which may progress to depression, circulatory and respiratory systems collapse, and death**.

Low doses of cholinesterase inhibitors, such as **physostigmine,** may be used to **overcome atropine toxicity**. Atropine may also induce troublesome urinary retention.

B. Scopolamine

It is one of the most effective **anti-motion sickness** drugs available. It also has the unusual effect of **blocking short-term memory**. Scopolamine produces **sedation**, but it can produce excitement at higher doses. Scopolamine may produce **euphoria** and is susceptible to abuse.

2. Therapeutic uses: The therapeutic use of scopolamine is limited to the **prevention of motion sickness and postoperative nausea and vomiting**.

C. Ipratropium and tiotropium

These agents are approved as bronchodilators for the maintenance treatment of **bronchospasm associated with chronic obstructive pulmonary disease (COPD).** Ipratropium is also used in the acute management of **bronchospasm in asthma**. Both agents are delivered **via inhalation**. Because of their positive charges, these drugs do not enter the systemic circulation or the CNS, isolating their effects on the pulmonary system. Tiotropium is administered once daily, a significant advantage over ipratropium, which requires dosing up to four times daily.

D. Tropicamide and cyclopentolate

These agents are used as **ophthalmic solutions for mydriasis and cycloplegia** (paralysis of the eye's ciliary muscle).

E. Benztropine and trihexyphenidyl

Useful as adjuncts with other **antiparkinsonian** agents to treat Parkinson’s disease and different types of parkinsonian syndromes, including antipsychotic-induced **extrapyramidal symptoms**.

F. Oxybutynin & Tolterodine

It is used to treat an overactive bladder. Bladder capacity is increased, and the frequency of bladder contractions is reduced. **Side effects** include dry mouth, constipation, and blurred vision, which limit the tolerability of these agents if used continually.

Ganglionic Blockers

Ganglionic blockers specifically act on the nicotinic receptors of both parasympathetic and sympathetic autonomic ganglia.

A. Nicotine

A component of cigarette smoke, nicotine, is a poison with many undesirable actions. **It is without therapeutic benefit** and is harmful to health. Depending on the dose, nicotine depolarizes autonomic ganglia, resulting first in **stimulation** and then **paralysis of all ganglia**. The stimulatory effects are complex and result from the increased release of neurotransmitters due to effects on both sympathetic and parasympathetic ganglia. **For example, enhanced dopamine release and norepinephrine may be associated with pleasure and appetite suppression**. The overall response of a physiologic system is a summation of nicotine's stimulatory and inhibitory effects. These include increased blood pressure and cardiac rate (due to transmitter release from adrenergic terminals and from the adrenal medulla) and peristalsis and secretions. **At higher doses**, the blood pressure falls because of the ganglionic blockade, and activity in both the GI tract and bladder musculature ceases.

Neuromuscular-blocking Agents

Neuromuscular blockers are clinically helpful **during surgery** to facilitate tracheal intubation and provide complete muscle relaxation at lower anaesthetic doses, allowing for more rapid recovery from anaesthesia and **reducing postoperative respiratory depression**.

A. Nondepolarizing (competitive) blockers (Mech of action)

Curare [kyoo- RAH-ree]. The neuromuscular-blocking agents have significantly **increased the safety** of anaesthesia because **less anaesthetic is required** to produce **muscle relaxation**, allowing patients to **recover quickly and completely** after surgery.

1. Mechanism of action: neuromuscular-blocking (**Nondepolarizing (competitive) blockers)**
2. Pharmacokinetics: All neuromuscular-blocking agents are **injected intravenously or occasionally intramuscularly since they are not effective orally.**
3. Adverse effects: These agents are generally **safe with minimal side effects.**

B. Depolarizing agents

Succinylcholine is the only depolarising muscle relaxant in use today.

1. Mechanism of action: Succinylcholine attaches to the nicotinic receptor and acts like ACh to depolarise the junction.
2. Actions: As with competitive blockers, **the respiratory muscles are paralyzed**. Succinylcholine initially produces brief muscle fasciculations (spontaneous contraction) that cause muscle soreness (pain).
3. Therapeutic uses: Because of its rapid onset of action, succinylcholine is useful when **rapid endotracheal intubation is required** during the induction of anaesthesia. It is also used during electroconvulsive shock treatment.
4. Pharmacokinetics: Succinylcholine is injected intravenously. Its brief duration of action results from redistribution and rapid hydrolysis by plasma pseudocholinesterase. Therefore, it is sometimes given by continuous infusion to maintain a more extended period of effect. Drug effects rapidly disappear upon discontinuation.
5. Adverse effects: Hyperthermia, Apnea, Hyperkalemia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Pharmacology

Dentistry College

TIKRIT UNIVERSITY

(2024-2025)

Year 3

Assistant lecturer

FARAH MOHAMMED NAJEEB

Adrenergic agonist and antagonist

- The adrenergic drugs affect receptors stimulated by norepinephrine (noradrenaline) or epinephrine (adrenaline). These receptors are known as **adrenergic receptors or adrenoceptors**.
- Adrenergic drugs that activate adrenergic receptors are termed **sympathomimetics**, and drugs that block the activation of adrenergic receptors are termed **sympatholytic**.
- Some sympathomimetics directly activate adrenergic receptors (**direct-acting agonists**), while others act indirectly by **enhancing release or blocking the reuptake of norepinephrine (indirect-acting agonists).**

Adrenergic receptors (adrenoceptors): Two main families of receptors, designated **α and β,** are classified based on their responses to the adrenergic agonist's epinephrine, norepinephrine, and isoproterenol.

Catecholamines

- **Epinephrine, norepinephrine, isoproterenol, and dopamine** are called **catecholamines**. These compounds share the following properties:
- Rapid inactivation: Catecholamines are metabolized by Catechol-O-methyltransferase (COMT) postsynaptically and by Monoamine oxidases (MAO) intraneuronally, as well as by COMT and MAO in the gut wall and by MAO in the liver. Thus, catecholamines have only a **brief period** of action when given **parenterally, and they are inactivated (ineffective) when administered orally.**
- Catecholamines are polar and, therefore, **DO NOT** readily penetrate the **CNS**.

Non-catecholamines

- Compounds have longer half-lives because COMT **does not inactivate them.**
- These include **phenylephrine, ephedrine, and amphetamine.**
- These agents are poor substrates for MAO (an essential route of metabolism) and, thus, show a **prolonged duration of action**. Increased lipid solubility of many of the non-catecholamines **permits greater access to the CNS.**

Mechanism of action of adrenergic agonists

1. Direct-acting agonists: These drugs act directly on α or β receptors, producing effects like those that occur following stimulation of sympathetic nerves or release of epinephrine from the adrenal medulla.
2. Examples of direct-acting agonists include epinephrine, norepinephrine, isoproterenol, and phenylephrine.
3. Indirect-acting agonists: These agents may **block the reuptake** of norepinephrine or cause the **release** of norepinephrine from the cytoplasmic pools or vesicles of the adrenergic neuron.
4. Examples of **reuptake inhibitors** and agents that cause norepinephrine **release** include **cocaine and amphetamines**, **respectively.**

3. Mixed-action agonists: **Ephedrine and pseudoephedrine** both **stimulate** adrenoceptors directly and **release** norepinephrine from the adrenergic neuron.

Direct-acting Adrenergic Agonists

Epinephrine: Epinephrine interacts with both **α and β receptors**. At **low doses**, **β effects** (**vasodilation**) on the vascular system predominate, whereas, **at high doses**, **α effects** (**vasoconstriction**) are the strongest.

Actions:

a. **Cardiovascular**: Epinephrine **strengthens** the contractility of the myocardium (**positive inotrope**: β1 action) and increases its **rate** of contraction (**positive chronotrope**: β1 action). Therefore, cardiac output increases. These effects increase oxygen demands on the myocardium. Epinephrine activates β1 receptors in the kidney to cause renin release. Renin is an enzyme involved in the production of angiotensin II, a **potent vasoconstrictor**.
b. **Respiratory**: Epinephrine causes powerful **bronchodilation** by acting directly on bronchial smooth muscle **(β2 action).** It also **inhibits the release of allergy mediators** such as **histamines from mast cells.**
c. **Hyperglycemia**: Epinephrine has a significant hyperglycemic effect because of increased glycogenolysis in the liver (β2 effect), increased release of **glucagon** (β2 effect), and a **decreased release of insulin (α2 effect).**
d. **Lipolysis**: **Epinephrine initiates lipolysis** through agonist activity on the β receptors of adipose tissue. Increased levels of cAMP stimulate a hormone-sensitive lipase, which hydrolyses triglycerides to free fatty acids and glycerol.

2. Therapeutic uses:

a. **Bronchospasm: Epinephrine** is the primary drug used in the **emergency treatment** of respiratory conditions (**bronchoconstriction)** and can be used in treating acute asthma and anaphylactic shock. Within a few minutes after subcutaneous administration, respiratory function dramatically improves. However, selective β2 agonists, such as **albuterol**, are favoured in the **chronic treatment of asthma** because of a **longer duration of action and minimal cardiac stimulatory effects.**

b. **Anaphylactic shock**: **Epinephrine** is the drug of choice for treating type I hypersensitivity reactions (including anaphylaxis) in response to allergens.

c. **Cardiac arrest:** Epinephrine may be used to restore cardiac rhythm in patients with cardiac arrest.

d. **Anaesthetics**: Local anaesthetic solutions may contain **low concentrations** of epinephrine. **Epinephrine dramatically increases the duration of local anaesthesia by producing vasoconstriction at the injection site.** This allows the local anaesthetic to persist at the injection site before being absorbed into the systemic circulation. Very weak epinephrine solutions can also be applied topically to vasoconstrict mucous membranes and control the oozing of capillary blood.

NOTE: In emergency situations, epinephrine is given intravenously (IV) for the most rapid onset of action.

3. Adverse effects:

- Epinephrine can produce adverse CNS effects that include **anxiety, fear, tension, headache, and tremor.**
- It can trigger cardiac arrhythmias, particularly if the patient is **receiving digoxin.**
- Epinephrine can also induce **pulmonary oedema**.
- Epinephrine may have **enhanced cardiovascular actions** in patients with **hyperthyroidism**, and the dose must **be reduced in these individuals. (**Patients with hyperthyroidism may have increased production of adrenergic receptors in the vasculature, leading to a hypersensitive response).
- Inhalation anaesthetics also sensitise the heart to the effects of epinephrine, which may lead to **tachycardia**.
- Epinephrine increases the release of endogenous stores of **glucose.**
- In diabetic patients, dosages of **insulin may have to be increased.**

Norepinephrine

1. **Cardiovascular actions:**

a. **Vasoconstriction**: Norepinephrine causes a rise in peripheral resistance due to intense vasoconstriction of most vascular beds, including the kidney (α1 effect). Both systolic and diastolic **blood pressures increase.**

b. **Baroreceptor reflex**: Norepinephrine increases blood pressure.

2. **Therapeutic uses**: Norepinephrine is used to treat shock because it increases vascular resistance and, therefore, increases blood pressure.

3. **Adverse effects:** These are like epinephrine. In addition, norepinephrine is a potent **vasoconstrictor and may cause blanching and sloughing of skin along an injected vein.**

Isoproterenol

- Isoproterenol is a direct-acting synthetic catecholamine that **stimulates both β1- and β2-adrenergic receptors.**
- Its non-selectivity is one of its **drawbacks** and the reason why it is rarely used therapeutically.
- Isoproterenol produces intense heart stimulation, increasing heart rate, contractility, and cardiac output.
- Isoproterenol is a potent **bronchodilator (β2 effect).** The use of isoproterenol has largely been replaced with other drugs. The adverse effects of isoproterenol are similar to those of epinephrine.

Dopamine

- **Dopamine is the immediate metabolic precursor of norepinephrine**. Dopamine can activate **α- and β-adrenergic receptors.**
- At higher doses, it causes **vasoconstriction by activating α1 receptors, whereas, at lower doses, it stimulates β1 cardiac receptors.**

1. Actions:

a. Cardiovascular: Dopamine exerts a stimulatory effect on the β1 receptors of the heart, having both **positive inotropic and chronotropic effects**.

b. Renal and visceral: Increasing blood flow to the kidneys and other viscera. Therefore, dopamine is clinically useful in treating shock, in which significant increases in **sympathetic activity might compromise renal function**.

2. Therapeutic uses: Dopamine is the **drug of choice for cardiogenic and septic shock** and is given by continuous infusion. It raises blood pressure by **stimulating the β1** receptors in the heart to increase cardiac output and **α1 receptors** in blood vessels to increase total peripheral resistance.

3. Adverse effects: Nausea, hypertension, and arrhythmias.

Dobutamine

- Dobutamine is a synthetic, direct-acting catecholamine that is a β1 receptor agonist.
- It increases cardiac rate and output with few vascular effects.
- Dobutamine is used to **increase cardiac output in acute heart failure.**
- Adverse effects are like epinephrine. Tolerance may develop with prolonged use.

Oxymetazoline

- Oxymetazoline is a direct-acting synthetic adrenergic agonist that **stimulates both α1- and α2-adrenergic receptors.**
- Oxymetazoline is found in many over-the-counter short-term nasal spray **decongestants**, as well as in **ophthalmic drops**, to relieve the **redness of the eyes associated with swimming, colds, and contact lenses.**
- Oxymetazoline directly stimulates α receptors on blood vessels supplying the nasal mucosa and conjunctiva, thereby producing vasoconstriction and decreasing congestion.
- It is **absorbed in the systemic circulation regardless of the route of administration** and may produce **nervousness, headaches, and trouble sleeping.**
- Local irritation and sneezing may occur with intranasal administration. **Rebound** congestion and dependence are observed with long-term use.

Phenylephrine

- Phenylephrine is a direct-acting, synthetic adrenergic drug that binds primarily **to α1 receptors.**
- Phenylephrine is a **vasoconstrictor** that raises both systolic and diastolic blood pressures.
- The drug **treats hypotension** in hospitalized or surgical patients.
- Large doses can cause **hypertensive headaches and cardiac irregularities**.
- Phenylephrine acts as a **nasal decongestant** when applied topically or taken orally.
- Phenylephrine has replaced **pseudoephedrine** in many oral decongestants since pseudoephedrine has been misused to make methamphetamine.
- Phenylephrine is also used in ophthalmic solutions **for mydriasis.**

Clonidine

- Clonidine is **an α2 agonist that is used for the treatment of hypertension**.
- It can also be used to minimize the symptoms that accompany withdrawal from **opiates, tobacco smoking, and benzodiazepines.**
- The most common side effects of clonidine are **lethargy, sedation, constipation, and xerostomia.**
- **Abrupt discontinuation** must be avoided to **prevent rebound hypertension.**

Albuterol and terbutaline

- Albuterol and terbutaline are **short-acting β2 agonists** used primarily as **bronchodilators** and administered by a metered dose.
- Albuterol is used for managing **acute asthma symptoms.**
- Terbutaline is also used **off-label** as a uterine relaxant to **suppress premature labour.**
- **The side effects** of these agents are **tremors,** but patients tend to develop tolerance to this effect. Other side effects include **restlessness, apprehension, and anxiety**. Monoamine oxidase inhibitors **(MAOIs)** also increase the risk of adverse cardiovascular effects, and concomitant use **should be avoided.**

Salmeterol and formoterol

- Salmeterol and formoterol are **long-acting β agonists that are β2 selective**.
- A single dose by a metered-dose inhalation device, such as a dry powder inhaler, provides sustained bronchodilation over 12 hours, compared with less than 3 hours for albuterol.

Mirabegron

- **Mirabegron is a β3** agonist that relaxes the detrusor smooth muscle and increases bladder capacity.
- It is used for patients with **overactive bladder.**
- Mirabegron may **increase blood pressure** and should not be used in patients with uncontrolled hypertension.
- It **increases levels of digoxin.**


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Indirect-acting Adrenergic Agonists

Indirect-acting adrenergic agonists cause the **release, inhibit the reuptake, or inhibit the degradation of epinephrine or norepinephrine.**

Amphetamine: The marked central stimulatory action of amphetamine is often mistaken by drug abusers. However, the drug can also **increase blood pressure** significantly by α1 agonist action on the vasculature, as well as β1-stimulatory effects on the heart.

Tyramine: Tyramine is not a clinically useful drug, but it is important because it is **found in fermented foods**, such as aged cheese. Normally, it is oxidized by MAO in the gastrointestinal tract, but if the patient takes MAOIs, it can precipitate **serious vasopressor episodes**.

Cocaine: Cocaine is unique among local anaesthetics in having the ability to **block** the sodium-chloride-dependent **norepinephrine transporter** required for cellular uptake of norepinephrine into the adrenergic neuron. Consequently, **norepinephrine accumulates** in the synaptic space, resulting in enhanced sympathetic activity and potentiation of the actions of epinephrine and norepinephrine. Therefore, **small doses of the catecholamines produce greatly magnified effects in an individual taking cocaine.** In addition, the **duration of action of epinephrine and norepinephrine is increased**. Like amphetamines, it can **increase blood pressure by α1 agonist actions and β stimulatory effects.**

Mixed-action Adrenergic Agonists

- Ephedrine and pseudoephedrine are mixed-action adrenergic agents.
- They not only **release stored norepinephrine** from nerve endings but also **directly stimulate both α and β receptors**. These drugs have a **long duration of action.**
- Ephedrine and pseudoephedrine have excellent **absorption orally and penetrate the CNS.**
- Ephedrine **raises systolic and diastolic blood pressures** by vasoconstriction and cardiac stimulation and can be **used to treat hypotension.**
- Ephedrine produces a **mild stimulation of the CNS**. This increases alertness, decreases fatigue and prevents sleep.
- It also improves athletic performance.
- Pseudoephedrine is primarily **used orally to treat nasal and sinus congestion**.
- Pseudoephedrine has been **illegally used to produce methamphetamine**.

The adrenergic antagonists

- The adrenergic antagonists are also called adrenergic blockers or sympatholytics.
- These drugs act by either **reversibly or irreversibly** attaching to the adrenoceptors, thus preventing activation by endogenous catecholamines.
- Numerous adrenergic antagonists have important roles in clinical medicine, primarily in treating diseases associated with the **cardiovascular system.**

α-Adrenergic Blocking Agents

Drugs that block α adrenoceptors profoundly **affect blood pressure**. [Note: β receptors, including **β1** adrenoceptors on the **heart**, are not affected by **α blockade**.] The α-adrenergic blocking agents, phenoxybenzamine and phentolamine, **have limited clinical applications**.

Phenoxybenzamine

- Phenoxybenzamine is nonselective, linking covalently to both α1 and α2 receptors. The block is irreversible and non-competitive, and the only way the body can overcome the block is to **synthesis new adrenoceptors, which requires a day or longer**.
- Therefore, the actions of phenoxybenzamine last about **24 hours**.

Actions: Cardiovascular effects: The drug has been **unsuccessful** in maintaining lowered blood pressure in hypertension and is **no longer used for this purpose**.

Therapeutic uses: Phenoxybenzamine is used in **treating pheochromocytoma (a small vascular tumor of the adrenal medulla, causing irregular secretion of epinephrine and norepinephrine, leading to attacks of raised blood pressure, palpitations, and headache).**

Adverse effects: Phenoxybenzamine can cause **postural hypotension, nasal stuffiness, nausea, and vomiting**.

Phentolamine

- In contrast to phenoxybenzamine, phentolamine produces a **competitive block of α1 and α2** receptors that lasts for approximately **4 hours** after a single injection.
- Like phenoxybenzamine, it produces **postural hypotension**.
- Phentolamine **triggers** arrhythmias and anginal pain, and phentolamine is **contraindicated in patients with coronary artery disease.**
- Phentolamine is used for the **short-term management of pheochromocytoma.**
- **Phentolamine is useful to treat hypertensive crisis due to abrupt withdrawal of clonidine and from ingesting tyramine-containing foods in patients taking monoamine oxidase inhibitors.**

Prazosin, terazosin, doxazosin, tamsulosin, and alfuzosin

- Prazosin, terazosin, and doxazosin are selective **competitive blockers of the α1 receptor.** Tamsulosin and alfuzosin are examples of other selective α1 antagonists indicated for the treatment of **benign prostatic hyperplasia (BPH).**

Therapeutic uses:

- The first dose of these drugs may produce an **exaggerated orthostatic hypotensive** response that can result in syncope **(fainting).**
- This action, termed a **"first-dose" effect**, may be minimised by adjusting the first dose to one-third or one-fourth of the normal dose and by giving the drug at bedtime.
- These drugs may **cause modest improvement in lipid profiles and glucose metabolism in hypertensive patients.**

Adverse effects

- α1-Blockers such as prazosin and doxazosin may cause **dizziness**, **nasal congestion, headache, drowsiness, and orthostatic hypotension**.
- An additive antihypertensive effect occurs when α1 antagonists are given with vasodilators such as nitrates or PDE-5 inhibitors (for example, sildenafil), thereby necessitating **cautious dose titration and use at the lowest possible doses**.
- Inhibition of ejaculation and retrograde ejaculation.

Yohimbine

Yohimbine is a **selective competitive α2-blocker**. Its use in treating erectile dysfunction. It is contraindicated in cardiovascular disease, psychiatric conditions, and renal because it may worsen these conditions.

B-adrenergic Blocking Agents

Propranolol: A nonselective β antagonist

Propranolol is the prototype β-adrenergic antagonist and blocks both β1 and β2 receptors.

Actions:

1.Cardiovascular: Propranolol diminishes cardiac output, having both **negative inotropic** and **chronotropic effects**.

2.Peripheral vasoconstriction: The reduced cardiac output produced by all β-blockers leads to **decreased blood pressure**. There is a gradual reduction of both systolic and diastolic blood pressures in hypertensive patients.

3.Bronchoconstriction: Blocking β2 receptors in the lungs of susceptible patients causes contraction of the bronchiolar smooth muscle. This can precipitate an exacerbation in patients with chronic obstructive pulmonary disease (COPD) or asthma. Therefore, β-blockers, particularly nonselective ones, are contraindicated in patients with COPD or asthma.

4.Disturbances in glucose metabolism: β blockade leads to **decreased glycogenolysis** and **decreased glucagon secretion**. Therefore, if propranolol is given to a diabetic patient receiving insulin, careful blood glucose monitoring is essential because pronounced hypoglycemia may occur after insulin injection. β-blockers also attenuate the normal physiologic response to hypoglycemia.

Therapeutic uses

1. **Hypertension:**

- Propranolol **does not reduce blood pressure** in people with normal blood pressure.
- Propranolol lowers blood pressure in hypertension by several different mechanisms of action.

2. **Angina pectoris:** Propranolol decreases the oxygen requirement of the heart muscle and, therefore, is useful in the chronic management of stable angina.

3.Myocardial infarction: Propranolol and other β-blockers have a protective effect on the myocardium. Thus, patients with one myocardial infarction appear to be protected against a second heart attack **by prophylactic use of β-blockers**.

4.Migraine: Propranolol effectively reduces migraine episodes when used **prophylactically.** It is one of the more useful β-blockers for this indication due to the **lipophilic nature that allows it to penetrate the CNS.**

5.Hyperthyroidism: Propranolol and other β-blockers can be used in acute hyperthyroidism (thyroid storm). β-blockers may be lifesaving in protecting against serious cardiac arrhythmias.

Adverse effects:

1. **Bronchoconstriction:** cause significant bronchoconstriction due to the blockade of β2 receptors
2. **Arrhythmias:** Treatment with β-blockers must **never be stopped abruptly** because of the risk of precipitating cardiac arrhythmias, which may be severe.
3. **Sexual impairment:** Ejaculation impairment in the male.
4. **Metabolic disturbances:** β Blockade leads to decreased glycogenolysis and decreased glucagon secretion.
5. **CNS effects:** Propranolol has numerous CNS-mediated effects, including depression, dizziness, lethargy, fatigue, weakness, visual disturbances, hallucinations, short-term memory loss, emotional lability, nightmares, and depression. Fewer CNS effects may be seen with more hydrophilic β-blockers (for example, atenolol) since they **do not cross the blood-brain barrier as readily.**
6. **Drug interactions:** Drugs that interfere with or **inhibit the metabolism** of propranolol, such as cimetidine, fluoxetine, paroxetine, and ritonavir, **may potentiate its antihypertensive effects**. Conversely, those that **stimulate or induce its metabolisms**, such as barbiturates, phenytoin, and rifampin, can **decrease its effects.**

Nadolol and timolol: Nonselective β antagonists

- Nadolol and timolol also block β1- and β2-adrenoceptors and are more potent than propranolol.
- Nadolol has a very long duration of action. **Timolol reduces the production of aqueous humor** in the eye. It is used topically in treating chronic **open-angle glaucoma.**

Treatment of glaucoma:

- β-blockers, such as topically applied timolol, betaxolol, or carteolol, are effective in diminishing intraocular pressure in glaucoma.
- The β-blockers are only used for the chronic management of glaucoma. In an acute glaucoma attack, pilocarpine is still the drug of choice for emergency lowering of intraocular pressure.

Acebutolol, atenolol, betaxolol, bisoprolol, esmolol, metoprolol, and nebivolol: Selective β_1 antagonists: Drugs that preferentially block the β1 receptors **minimise the unwanted bronchoconstriction (β2 effect) seen with propranolol use in asthma patients.**

Actions: These drugs lower blood pressure in hypertension and increase exercise tolerance in angina.

Therapeutic uses:

- The **cardioselectivity β-blockers** are useful in **hypertensive patients** with impaired pulmonary function. These agents are also first-line therapy for chronic **stable angina**.
- Bisoprolol and the extended-release formulation of metoprolol are indicated for **managing chronic heart failure**.
- Because these drugs have less effect on peripheral vascular β2 receptors, **coldness of extremities (Raynaud phenomenon), a common side effect of β-blockers, is less frequent.**

Acebutolol and pindolol: Antagonists with partial agonist activity

Cardiovascular: Acebutolol (β1-selective antagonist) and pindolol (nonselective β-blocker) are not pure antagonists. These drugs also have the ability to **weakly stimulate both β1 and β2 receptors.** The result of these opposing actions is a diminished effect on the cardiac rate and cardiac output.

Therapeutic use in hypertension: effective in hypertensive patients with moderate bradycardia because a further decrease in heart rate is less pronounced with these drugs.

Labetalol and carvedilol: Antagonists of both α and β adrenoceptors

Actions: Labetalol and carvedilol are nonselective β-blockers with concurrent α1-blocking actions that **produce peripheral vasodilation**, thereby **reducing blood pressure**.

Therapeutic use in hypertension and heart failure: Labetalol is employed as an alternative to methyldopa in treating pregnancy-induced hypertension. Intravenous labetalol is also used to **treat hypertensive emergencies**.

Adverse effects: Orthostatic hypotension and dizziness are associated with α1 blockade.

Drugs Affecting Neurotransmitter Release Or Uptake

Reserpine, a plant alkaloid, **blocks** the Mg^{2+} /adenosine triphosphate–dependent transport of biogenic amines (norepinephrine, dopamine, and serotonin) from the cytoplasm into storage vesicles in the adrenergic nerve terminals in all body tissues. **Reserpine has a slow onset, and a long duration of action**. **It has been used for managing hypertension** but has largely been replaced with newer agents with better side effect profiles and fewer drug interactions.


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Antihypertensive drugs

1. **ACE inhibitors:** Captopril, Enalapril, Lisinopril, Perindopril, Ramipril.
2. **Angiotensin II receptor antagonists:** Losartan, Candesartan, Irbesartan, Valsartan.
3. **Calcium channel blockers:** Diltiazem, Verapamil, Nifedipine, Amlodipine, Nicardipine, Isradipine, Felodipine.
4. **Diuretics:**

a. Thiazides and related agents: Chlorothiazide, Hydrochlorothiazide, Chlorthalidone, Indapamide.
b. Loop diuretics: Furosemide, Bumetanide, Torsemide.
c. Potassium-sparing diuretics: Amiloride, Triamterene, Spironolactone.

5. Sympatholytic agents

a. Centrally acting adrenergic drugs: Clonidine, Methyldopa.
b. β Adrenergic blockers: Atenolol, Metoprolol, Esmolol, Propranolol, Timolol.
c. β Adrenergic blockers with additional α -blocking activity: Labetalol, Carvedilol.
d. α Adrenergic blockers:

- **Selective:** Prazosin, Terazosin, Doxazosin.
- **Non-selective:** Phenoxybenzamine, Phentolamine.

6. Vasodilators

a. Arteriolar: Hydralazine, Minoxidil, Diazoxide.
b. Arteriolar and venodilator : Sodium nitroprusside.

Mechanism of action

Angiotensin converting enzyme inhibitors:

a. Inhibit the generation of angiotensin II resulting in:
   - Dilatation of arterioles → ↓ peripheral vascular resistance (PVR) → ↓BP.
   - Decrease in aldosterone production → decrease in Na^+ and H_2O retention → ↓BP.
   - Decrease in sympathetic nervous system activity.

b. Inhibit the degradation of bradykinin, which is a potent vasodilator.

c. Stimulate synthesis of vasodilating prostaglandins through bradykinin.

All these actions contribute to their antihypertensive effect.

Adverse effects and contraindications

1.Cough (**dry cough**) is due to increased bradykinin levels in the lungs (indication to stop the drug).

2.Angioedema

3.Proteinuria.

4.Teratogenic effect (contraindicated in pregnancy).

5.Severe hypotension.

6.Neutropenia.

7.Rashes & Itching.

8.Loss of taste sensation and nausea.

In patients receiving ACE inhibitors, **hyperkalemia** may occur in the presence of renal insufficiency or when combined with potassium-sparing diuretics.

Therapeutic uses of ACE inhibitors

1.Hypertension: especially in patients with diabetes and congestive heart failure (CHF). They are preferred in patients with diabetes because they delay or prevent the progression of renal complications.

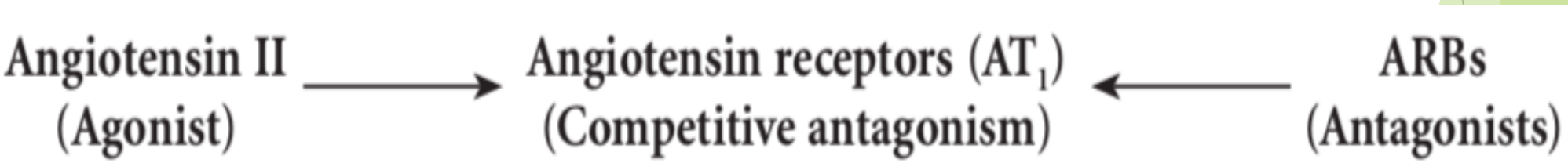
2. Congestive cardiac failure.

3. Acute myocardial infarction.

4. Diabetic nephropathy.

Angiotensin Receptor Blockers (ARBs) or Angiotensin Receptor Antagonists

The two types of angiotensin II-receptors are AT_1 and AT_2. Most of the effects of angiotensin II are mediated by AT1 receptors. They are vasoconstriction, aldosterone secretion and noradrenaline release from sympathetic nerve endings. The role of AT_2 receptors is not known.



Uses

Angiotensin receptor blockers are used in **hypertension, congestive cardiac failure (CCF), MI and diabetic nephropathy.**

Adverse effects

Angiotensin receptor blockers are better-tolerated as compared to ACE inhibitors. They cause **headache, hypotension, weakness, rashes, nausea, vomiting and teratogenic effects.** They **may cause hyperkalaemia** in patients with **renal failure or in patients on K+-sparing diuretics.** They are **less likely** to produce cough or angioedema than ACE inhibitors.

Diuretics

Thiazide diuretics: These are used in uncomplicated mild-to-moderate hypertension and have a **long duration of action.**

Potassium-sparing diuretics are usually given with thiazides **to counteract K^+ loss and increase antihypertensive efficacy**. ACE inhibitors with thiazides decrease K^+ loss by thiazides and enhance the antihypertensive effect.

Adverse effects

They are hypokalaemia, hyperglycaemia, hyperuricaemia, hyperlipidaemia, hypercalcaemia, impotence and decreased libido.

Potassium Sparing Diuretics

1. **Directly acting (Amiloride, Triametrine)**

- **Amiloride** acts by inhibiting Na^+ reabsorption in the late distal tubules & collecting ducts.
- **Amiloride** has mild diuretic effects:
- Side effects: Hyperkalemia
- This drug is mainly combined with Thiazides or loop diuretics so that the incidence of hyperkalemia & hypokalemia is decreased.

2. **Aldosteron antagonists**

- **Spironolactone (Aldactone):** It is an aldosterone receptor antagonist, so it inhibits Na^+ reabsorption & inhibits K^+ excretion; therefore, it causes hyperkalemia.
- It has antiandrogen activity, and it causes male sexual dysfunction (Erectile dysfunction) & Gynecomastia (enlarged breast tissue in men)

• Used for: Hypertension, Heart failure, Severe acne, Hirsutism, Polycystic ovary, Hyperaldosteronism.

Loop Diuretics (Furosemide, Bumetanide, Torsemide)

These drugs have a **short duration of action.** They are primarily used in medicine to treat hypertension and oedema, often due to congestive heart failure or chronic kidney disease. Side effects include increased urination and sodium loss, hypokalemia, dizziness, lightheadedness, headache, blurred vision, dehydration and electrolyte imbalance, and temporary or permanent decreased hearing/deafness.

Calcium Channel Blockers (CCBs) are helpful in **all grades of hypertension. (**Diltiazem, Verapamil, Nifedipine, etc.)

The antihypertensive effect is mainly **due to peripheral vasodilatation.** Dihydropyridines (DHPs) are more likely to cause headache, flushing, palpitation and reflex tachycardia.

Sympatholytics

β -Adrenergic Blockers

➢ **β**-Blockers are effective in all grades of hypertension.

- Selective **β**-blockers (block only β_1), e.g., Atenolol, Metoprolol, Esmolol, etc.
- Non-selective **β**-blockers (block both β_1 and β_2), e.g., Propranolol and Timolol.

➢ **B** –Blockers are mainly useful in the:

- Young hypertensives with high renin levels.
- Patients with associated conditions, such as angina, post-MI, migraine and psychosomatic disorders.
- Patients are receiving vasodilators to counteract reflex tachycardia.

➢ **β**-Blockers may precipitate **CCF and bronchospasm** in susceptible individuals. They must be used with **caution** in people with diabetes receiving hypoglycaemic drugs. **Sudden stoppage** of **β**-blockers after prolonged therapy can produce withdrawal syndrome due to sympathetic overactivity.

Centrally Acting Sympatholytics

➢ **Clonidine:** Clonidine is a centrally-acting antihypertensive drug.

- **Adverse effects:** Dryness of mouth and eyes, sedation, depression, bradycardia, impotence, nausea, dizziness, parotid gland swelling and pain.
- **Sudden stoppage** of clonidine after prolonged use may cause withdrawal syndrome: headache, nervousness, tachycardia, sweating, tremors, palpitation, and rebound hypertension.

➢ **Uses**

- In hypertension.
- To treat withdrawal symptoms in **opioid and alcohol addicts.**
- As a pre-anaesthetic agent.
- As antidiarrhoeal in diabetic neuropathy (Idiopathic diarrhoea)? Stimulation of alpha 2-adrenergic receptors on enterocytes promotes fluid and electrolyte absorption and inhibits anion secretion.

α –Methyldopa

It is a centrally acting sympatholytic agent. **α-**Methyl noradrenaline is a false transmitter released during nerve stimulation instead of noradrenaline. **α-**Methyl noradrenaline acts by stimulating α_2-receptors in vasomotor centre (VMC).

Adverse effects

These include nasal stuffiness, headache, sedation, **mental depression**, dry mouth, bradycardia, **impotence, gynaecomastia**, hepatitis and rarely haemolytic anaemia.

Clonidine and **α**-methyldopa are usually employed as the second or third-line agents in hypertension because of a **high incidence of side effects**. α-Methyldopa is one of the preferred antihypertensive drugs during pregnancy.

α -Adrenergic Blockers

- **Nonselective α-blockers** are not preferred for essential hypertension. They treat hypertension in special conditions like **pheochromocytoma, clonidine withdrawal and cheese reaction**.

- **Selective α-blockers:** Prazosin causes the **first-dose phenomenon, postural hypotension after the first dose**. Therefore, the initial dose should be small (1 mg) and usually given at bedtime so that the patient remains in bed for several hours, reducing the risk of fainting attacks.
- **Terazosin and doxazosin are longer-acting than prazosin, given once daily in the treatment of hypertension**.

Vasodilators

- **Minoxidil:** It is a potent arteriolar dilator. Minoxidil is used with a **β**-blocker and a diuretic. Topical minoxidil is used to promote hair growth in the male type of baldness.

- **Hydralazine:** It is a directly acting arteriolar dilator. The side effects are reflex **tachycardia, palpitation**, and sodium and water retention, which can be **countered by combining hydralazine with a diuretic and a β-blocker**. Other side effects are headache, hypotension, flushing, angina, myocardial infarction, coronary steal phenomenon, etc.

- **Sodium Nitroprusside:** It is a powerful arteriolar and vasodilator. Sodium nitroprusside is the drug of choice for **hypertensive crisis**; it can also be used to improve cardiac output in CCF. **Nitroprusside can cause severe hypotension**; hence close monitoring of BP is required. Prolonged administration may cause anorexia, nausea, vomiting, fatigue, disorientation, and toxic psychosis due to cyanide accumulation, which may lead to severe lactic acidosis.

Angina

Treatment is aimed at maintaining the balance between O_2 supply and demand.

Classification

1. **Nitrates**: Nitroglycerin (glyceryl trinitrate), isosorbide dinitrate, isosorbide mononitrate, erythritol tetranitrate.
2. **β -Adrenergic blockers**: Propranolol, Metoprolol, Atenolol.
3. **Calcium channel blockers (CCBs)**: Verapamil, Diltiazem, Nifedipine, Felodipine, Amlodipine, Nitrendipine, Nimodipine.
4. **Potassium channel opener**: Nicorandil.
5. **Others**: **A**ntiplatelet agents (low-dose aspirin, Clopidogrel), Statins.

Organic Nitrates: Nitrates are mainly venodilators, and also cause arteriolar dilatation, therefore, reducing both preload and afterload. **On vascular smooth muscle:** Nitroglycerin (Sublingual) quickly relieves anginal pain by decreasing the O2 requirement and increasing the O2 delivery to the myocardium.

Adverse effects: Adverse effects are due to extensive vasodilatation. They are headache, postural hypotension, tachycardia, palpitation, weakness, flushing and rarely syncope. The tablet may spit out after the pain is relieved to avoid these symptoms. Overdosage may cause methemoglobinemia.

- **Tolerance** to nitrates occurs on prolonged use. They also exhibit cross-tolerance.

Isosorbide dinitrate can be used sublingually for acute anginal attacks and orally for chronic prophylaxis.
Isosorbide mononitrate: It is preferred over dinitrate for chronic prophylaxis of angina because it has:

- Longer duration of action.
- High oral bioavailability as it does not undergo first-pass metabolism.

Drugs Used In Congestive Cardiac Failure (CCF)

Classification

Diuretics

a. Loop diuretics: Furosemide, Bumetanide.
b. Thiazide diuretics: Chlorothiazide, Hydrochlorothiazide.
c. Aldosterone antagonist: Spironolactone.

Vasodilators

a. ACE inhibitors: Enalapril, Lisinopril, Ramipril.
b. Angiotensin-receptor blockers (ARBs): Losartan, Candesartan.
c. Sodium nitroprusside.
d. Nitroglycerin, Isosorbide dinitrate.
e. Hydralazine.

β-Adrenergic blockers: Metoprolol, Bisoprolol, Carvedilol.
Sympathomimetic amines: Dopamine, Dobutamine.
Cardiac glycosides: Digoxin.
Phosphodiesterase inhibitors: Inam rinone, Milri none.

Digoxin (Cardiac Glycosides)

Pharmacological actions: **Cardiac actions**

- Indirect action by stimulating vagus (vagomimetic effect).

Adverse effects

Digoxin has a narrow margin of safety. Monitoring serum digoxin, electrolyte levels and electrocardiogram (ECG) are essential during digitalis therapy.

- GIT: Early symptoms of toxicity are anorexia, nausea and vomiting, which are due to GI irritation and CTZ stimulation.
- CNS: effects include headache, confusion, restlessness, disorientation, weakness, and visual disturbances.
- Skin rashes and gynaecomastia can occur occasionally.
- Digitalis can cause arrhythmias.

Sympathomimetic Amines

Dopamine and dobutamine are used in acute heart failure; they provide symptomatic relief in patients with ventricular dysfunction.

Dopamine: Stimulates β_1-receptors of the heart and increases myocardial contractility and cardiac output, but tachycardia is less prominent. Dopamine is used in cardiogenic shock and acute heart failure with renal impairment. It improves both cardiac and renal function.

Dobutamine: It has a selective inotropic effect and increases cardiac output. The side effects are tachycardia, a rise in BP and the development of tolerance.

Phosphodiesterase Inhibitors

Inamrinone and milrinone exert both positive inotropic and vasodilator actions. They are administered intravenously. They are used for short-term treatment of severe heart failure. The adverse effects of inamrinone include nausea, vomiting, arrhythmias, thrombocytopenia and hepatotoxicity. Milrinone is more potent than inamrinone and does not produce thrombocytopenia.

Shock

Shock occurs when there is a severe decrease in tissue perfusion. The important manifestations of shock are hypotension, tachycardia, thready pulse, pale, cold and clammy skin, hypoventilation, oliguria, clouding of consciousness, etc.

Hypovolaemic Shock

Achieve haemostasis in case of haemorrhagic shock. Intravenous fluids to restore the loss, e.g. dextrose, normal saline, Ringer lactate, dextran, etc. Blood transfusion in case of acute haemorrhage.

Anticoagulants

Anticoagulants are drugs that prevent or reduce the coagulability of blood.

a. Parenteral anticoagulants

- **Heparin**.
- Low-molecular-weight heparins: **Enoxaparin (Enoxa-parin).**
- Direct thrombin inhibitors: **Lepirudin (Lepi-rudin)**.

b. Oral anticoagulants

- Coumarin derivatives: **Warfarin, Dicumarol**.
- **Phenindione (Phenin-dione)**.
- **Dabigatran etexilate (Dabi-gatran etexi-late)**.

Mode of administration

Heparin is administered by i.v. Infusion and i.v. Intermittent injection (for treatment) or s.c. route (for prophylaxis). Administration of heparin intramuscularly may cause haematomas; hence, this route should not be used.

Adverse effects and contraindications

- **Bleeding**: Heparin has a narrow therapeutic dose range bleeding is the main side effect. Overdosage may cause severe and fatal haemorrhage. **Protamine sulphate** is a specific **heparin antagonist** obtained from fish sperm.
- Heparin-induced thrombocytopenia (HIT).
- Hypersensitivity reactions can occur rarely.
- Osteoporosis.
- Reversible alopecia has been reported.

➢ **H**eparin is contraindicated in **h**aemophiliacs, patients with heparin-induced thrombocytopenia (**H**IT), severe **h**ypertension, intracranial **h**aemorrhage, bacterial endocarditis, active tuberculosis, peptic ulcer, threatened abortion, cirrhosis, renal failure, etc.

Oral Anticoagulants

Among oral anticoagulants, **coumarin** derivatives are commonly used. Oral anticoagulants act only in vivo. They are vitamin K antagonists.

Adverse effects

- **Bleeding:** Bleeding is the most critical and common side effect of warfarin. Bleeding can occur anywhere: skin, pulmonary, gastrointestinal and urinary tract, cerebral, hepatic, uterine, etc. Bleeding can be controlled by oral or parenteral vitamin K1 (depending on severity).
- **Teratogenic effect:** Warfarin is contraindicated during pregnancy as it may cause foetal CNS abnormalities, foetal haemorrhage, abortion or intrauterine death.
- **Skin necrosis** is a rare complication that occurs within the first week of therapy. The skin lesions are commonly seen on the breast, buttocks, abdomen and thighs.
- **Other rare side effects:** Include diarrhoea, alopecia, urticaria, dermatitis, abdominal cramps and anorexia.

Fibrinolytics (Thrombolytics)

Fibrinolytics promote the conversion of plasminogen to plasmin. Streptokinase, urokinase, alteplase, reteplase and tenecteplase are plasminogen activators.

Uses of fibrinolytic

1. **Acute MI**: The main aim of fibrinolytic therapy is to restore coronary artery patency. These drugs dissolve the clot by promoting the conversion of plasminogen to plasmin. Thrombolytic treatment is more effective if administered within 6–12 h of the onset of symptoms.
2. **Deep vein thrombosis**: Thrombolytic therapy helps to prevent pulmonary embolism.
3. **Pulmonary embolism**: Fibrinolytics are used to lyse the clot.

Contraindications

These include recent trauma, recent surgery, recent abortion, recent stroke, severe hypertension, severe diabetes, severe liver damage, peptic ulcer and bleeding disorders.

Fibrinolytic inhibitors:

Antifibrinolytics block the conversion of plasminogen to plasmin and thus inhibit fibrinolytic activity.

Amino-caproic acid (ACA)

It is administered orally or intravenously. It is used mainly to control bleeding due to an overdose of fibrinolytic after tooth extraction and surgery in haemophiliacs. It can also be used in haematuria and bleeding following obstetric complications. It rarely causes myopathy and muscle necrosis.

Tranexamic acid : It is available for oral, i.v. And topical administration. It is more potent than ACA. It controls bleeding due to excessive fibrinolytic activity following a tooth extraction, tonsillectomy, prostatectomy, etc. In dentistry, tranexamic acid-soaked gauze or mouthwash can reduce bleeding postoperatively in haemophiliacs and patients on anticoagulant therapy. Its main side effects are nausea, vomiting, diarrhoea, headache, etc.

Antiplatelet Drugs

Drugs that inhibit platelet aggregation are called antiplatelet drugs.

Classification

1. Low-dose aspirin.
2. Dipyridamole.
3. Ticlopidine and clopidogrel.
4. Abciximab, eptifibatide and tirofiban.

Aspirin (TXA2 synthesis inhibitor) Low-dose aspirin (50–325 mg) irreversibly acetylates platelet COX-I and reduces the production of TXA2; thus, the antiplatelet effect lasts for the lifetime of the platelets, i.e., 7–10 days. In higher doses, aspirin inhibits both TXA2 and PGI2; hence efficacy is reduced. Common adverse effects are gastric irritation and bleeding.

Dipyridamole (phosphodiesterase inhibitor)

It is a vasodilator. It inhibits phosphodiesterase and increases cyclic adenosine monophosphate (cAMP) levels, inhibiting platelet aggregation. It is occasionally used in combination with warfarin in patients with prosthetic heart valves during the postoperative period.

Ticlopidine and Clopidogrel

They inhibit adenosine diphosphate (ADP)-mediated platelet aggregation. It has a long-duration of antiplatelet effect. Side effects are nausea, vomiting, diarrhoea, leukopenia, agranulocytosis, thrombocytopaenia and GI bleeding. Clopidogrel is a congener of ticlopidine.

Abcixi-mab, eptifi-batide and tiro-fiban

These drugs are administered parenterally. The main side effect of these drugs is bleeding.

Uses

1. Acute MI**:** Low-dose aspirin is most commonly used in high-risk individuals to reduce the incidence of MI and in post-MI patients to prevent recurrent attacks.
2. They can also be used in unstable angina, transient ischaemic attacks, patients with prosthetic heart valves, etc.

Antihyperlipidemic Agents

Classifications include **Fibrates, HMG CoA reductase inhibitors, Cholesterol absorption inhibitors, Bile-acid, and Nicotinic acid**.

A- Fibrates: Gemfibrozil, Fenofibrate, Clofibrate

Pharmacological Action: Decrease in triglyceride levels and increase in HDL.

Therapeutic Uses

- Reduction of plasma triglycerides (VLDL)
- Increased levels of HDL

Adverse effects: GI distress, Gallbladder stones, Myopathy (muscle tenderness, pain), Hepatotoxicity

B- HMG CoA Reductase Inhibitors (Statins): Atorvastatin, Simvastatin, Lovastatin, Pravastatin, Rosuvastatin, Fluvastatin

Pharmacological Action: Decrease manufacture of LDL, Decrease manufacture of VLDL & Increase manufacture of HDL

Therapeutic uses: Primary hypercholesterolemia, Prevention of coronary events, Protection against MI and stroke for clients with diabetes & Increasing levels of HDL in clients with primary hypercholesterolemia

Adverse effects: Hepatotoxicity, Myopathy and Peripheral neuropathy

Interactions:

- Fibrates (gemfibrozil, fenofibrate) and Ezetimibe increase the risk of Myopathy.

-**Grapefruit juice suppresses** CYP3A4 and can increase levels of Statins.

C- Cholesterol Absorption Inhibitor: Ezetimibe

Pharmacological Action: Inhibits absorption of cholesterol secreted in the bile and from food.

Therapeutic Uses:

- Patients with modified diets can use this medication as an adjunct to help lower LDL cholesterol.
- Medication can be used alone or in combination with a statin medication.

Adverse effects: Hepatitis and Myopathy

D- Bile-Acid: Cholestyramine

Pharmacological Action: Decrease in LDL cholesterol

Therapeutic Use: These medications are used as adjuncts with an HMG CoA reductase inhibitor, such as atorvastatin, and with dietary measures to lower cholesterol levels.

Adverse effects

- Cholestyramine may cause GI distress and decrease the absorption of fat-soluble vitamins.
- Constipation.

E- Nicotinic Acid : Niacin

Pharmacological Action: Decrease in LDL cholesterol and triglyceride levels

Therapeutic Uses

- For clients at risk for pancreatitis and elevated triglyceride levels
- To lower elevated LDL cholesterol and triglycerides and to raise HDL levels

Adverse effects: GI distress, Facial flushing, Hyperglycemia, Hepatotoxicity, Hyperuricemia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Pharmacology

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SEDATIVES AND HYPNOTICS

Classification of sedatives and hypnotics

- **Benzodiazepines:** Diazepam, Oxazepam, Lorazepam, Flurazepam, Nitrazepam, Clonazepam, Chlordiazepoxide, Alprazolam.

- **Barbiturates:**

Long-acting: Phenobarbitone, Mephobarbitone.
Short acting: Pentobarbitone, Secobarbitone.
Ultra-short acting: Thiopentone.

- **Non-benzodiazepine hypnotics:** Zolpidem.
- **Miscellaneous:** Chloral hydrate, promethazine, neuroleptics, opioids, etc.

BENZODIAZEPINES

Mechanism of action: Benzodiazepines facilitate the action of gamma-aminobutyric acid (GABA): **they potentiate the inhibitory effects of GABA.**

Pharmacological actions and therapeutic uses

1. **Sedation and hypnosis**
2. **Anticonvulsant**
3. **Pre-anaesthetic medication**
4. **Antianxiety (anxiolytic) effect**
5. **Muscle relaxant (centrally acting)**
6. **To treat alcohol withdrawal symptoms**.

Adverse effects: Benzodiazepines: The common side effects are **drowsiness, confusion, blurred vision, amnesia, disorientation, tolerance and drug dependence**.

Withdrawal after chronic use causes symptoms like **tremors, insomnia, restlessness, nervousness and loss of appetite.**

BARBITURATES

Mechanism of action: Barbiturates have GABA-facilitatory action—they potentiate the inhibitory effects of GABA.

Pharmacological actions and uses

1. **Sedation and hypnosis**
2. **General anaesthesia (GA)**
3. **Anticonvulsant**

Adverse effects

- The common side effects are drowsiness, confusion, headache, ataxia, hypotension and respiratory depression.
- Hypersensitivity.
- Tolerance.
- Physical and psychological dependence develops on repeated use.
- Prolonged use of phenobarbitone may cause megaloblastic anaemia.

NON-BENZODIAZEPINE HYPNOTICS

Zolpidem: Zolpidem mainly produces a hypnotic effect: it decreases sleep latency and increases sleep time duration in insomnia. The common side effects are headache, confusion, nausea and vomiting.

General anaesthesia in dental practice

Depending on the health status of the individual and the nature of the dental procedure to be undertaken, general anaesthesia, when indicated, can be administered as:

- Dental chair anaesthesia (on an outpatient basis).
- Daycare anaesthesia (patient is admitted and discharged on the same day) for oral surgical procedures lasting less than one h.
- Inpatient anaesthesia for extensive procedures.

Parenteral General Anaesthetics: Inducing Drugs

Thiopentone Sodium: It is an ultra-short-acting barbiturate. It is a commonly used i.v. anaesthetic for induction of anaesthesia. After a single i.v. dose, it rapidly enters highly perfused organs like the brain, liver, heart, etc., producing anaesthesia.

Uses: Thiopentone sodium is used for induction of anaesthesia.

Advantages of thiopentone: Rapid induction of anaesthesia and rapid recovery.

Disadvantages/adverse effects of thiopentone

- It depresses the respiratory centre.
- Depresses the vasomotor centre and myocardium.
- Causes laryngospasm

Complications of general anaesthesia

- Hypoxia
- Nausea, vomiting
- Dislocation of temporomandibular joint
- Persisting sedation
- Cardiac arrhythmias, especially with halothane
- Subcutaneous emphysema of the face can occur rarely.
- Hyperthermia

Local anaesthetics

Local anaesthetics (LAs) are the drugs that block nerve conduction when applied topically or injected locally and cause a reversible loss of all sensation in part supplied by the nerve.

Injectable anaesthetics

- Short-acting with low potency: **Procaine, Chloroprocaine**.
- Intermediate-acting with intermediate potency: **Lignocaine.**
- Long-acting with high potency: **Tetracaine.**

Mechanism of action: The cell membrane is the main site of action of local anaesthetics. Block the voltage-gated Na^+ channels.

Combination of vasoconstrictor with local anaesthetic

The commonly used vasoconstrictor with a local anaesthetic:

- **Adrenaline:** The addition of a vasoconstrictor (e.g., adrenaline) to the LA has the following **advantages:**

1. Slow absorption from the local site results in a prolonged duration of action of local anaesthesia.
2. Decreased bleeding in the surgical field.
3. Slow absorption of LA reduces its systemic toxicity.

General Adverse effects of Local anaesthetics

1. Central Nervous System (CNS): LAs initially cause CNS stimulation followed by depression.
2. CVS: Bradycardia, hypotension, cardiac arrhythmias.
3. Allergic reactions.
4. Mucosal irritation (cocaine) and methaemoglobinaemia (prilocaine) may be seen.

Antiepileptic Drugs (Antiseizure)

Epilepsy is a disorder of brain function characterized by paroxysmal cerebral dysrhythmia.

Clinical classification of antiepileptic drugs

Phenytoin is one of the most commonly used antiepileptic drugs. It has a selective antiepileptic effect and does not produce significant drowsiness.

Phenytoin is used for the treatment of:

- Generalized tonic-clonic seizures (grand mal epilepsy).
- Partial seizures.
- Trigeminal and other neuralgias.
- Status epilepticus: Phenytoin is administered intravenously in normal saline.

The adverse effects are:

- Hypertrophy and Hyperplasia of gums: Seen on chronic therapy and can be minimized by proper oral hygiene.
- Hypersensitivity reactions.
- Hirsutism.
- Hyperglycaemia.
- Megaloblastic anaemia.
- Osteomalacia.
- Hypocalcaemia.
- Foetal Hydantoin syndrome: Cleft lip, cleft palate, digital Hypoplasia, etc., due to the use of phenytoin during pregnancy.

Carbamazepine

Uses

1. Carbamazepine is one of the most commonly used antiepileptic drugs.
2. Carbamazepine is the drug of choice in treating trigeminal and other neuralgias; it is also useful in other neuropathic disorders.
3. Carbamazepine is used in the treatment of acute mania and bipolar disorder.

Adverse effects: Include sedation, drowsiness, vertigo, ataxia, diplopia, blurred vision, nausea, vomiting and confusion. Hypersensitivity reactions are skin rashes, eosinophilia, lymphadenopathy and hepatitis.

Oxcarbazepine: Is an analogue of carbamazepine.

Phenobarbitone: **Uses:** It is the cheapest antiepileptic drug. It is also useful in the prophylactic treatment of febrile convulsions. Also, can be used in status epilepticus.

The most common side effect of phenobarbitone is sedation. The other side effects are nystagmus, ataxia, confusion, megaloblastic anaemia and skin rashes.

Valproic Acid (Sodium Valproate):

Sodium valproate is a broad-spectrum antiepileptic drug.

Uses: Sodium valproate is highly effective in absence, myoclonic, partial and generalized tonic-clonic seizures. Other uses of valproate include mania and bipolar disorder.

1. **The common side effects** related to the GI tract are nausea, Vomiting, Anorexia and abdominal discomfort.
2. **CNS side effects** include sedation, ataxia and Tremor.
3. **Teratogenicity**: Orofacial and digital abnormalities; neural tube defects with increased incidence of spina bifida, so it should not be given during pregnancy.

Diazepam, Lorazepam, Clonazepam (Benzodiazepines)

Diazepam and lorazepam are effective in controlling status epilepticus. Clonazepam, a long-acting benzodiazepine, is used in the absence and myoclonic seizures. Intravenous diazepam is used to treat status epilepticus, tetanus, eclamptic convulsions, febrile convulsions, drug-induced convulsions, etc. Diazepam has a rapid onset but a short duration of action; hence repeated doses are required. Diazepam can be administered rectally in children during an emergency. Lorazepam has a rapid onset and long duration of action; therefore, preferred in status epilepticus.

Gabapentin

It is an analogue of GABA. It freely crosses BBB and acts by releasing GABA. There is no enzyme-inducing property, so drug interactions are rare. It is mainly used as an adjunct in partial seizures. It is also useful in migraine prophylaxis, diabetic neuropathy, bipolar disorder and post-herpetic neuralgias. The common side effects are sedation, ataxia, fatigue, headache and tremor.

OPIOID ANALGESICS

Classification of opioids

1. **Opioid agonists:** Morphine, codeine, Heroin, hydromorphone, oxymorphone, Pethidine, tramadol, methadone, dextropropoxyphene, fentanyl.
2. **Opioid agonist–antagonists**: Pentazocine, butorphanol.
3. **Partial μ-receptor agonist**: Buprenorphine.

Opioid Receptor; The three main types of opioid receptors are **μ** (mu), k (kappa) and δ (delta).

Therapeutic Uses of Morphine and its Congeners (same category)

1. As analgesic.
2. Pre anaesthetic medication:
3. Acute pulmonary oedema (cardiac asthma / coughing or wheezing).
4. Post-anaesthetic shivering: Pethidine is effective.
5. Cough: Codeine, pholcodine, dextromethorphan, etc., commonly suppress dry cough.
6. Diarrhoea: Synthetic opioids such as diphenoxylate and loperamide are used for the symptomatic treatment of diarrhoea.

Adverse effects

1. Nausea, vomiting and constipation.
2. Respiratory depression.
3. Hypotension due to vasodilatation.
4. Drowsiness, confusion and mental clouding.
5. Itching (due to histamine release) and skin rashes.
6. Difficulty in micturition.
7. Respiratory depression.
8. Drug tolerance
9. Drug dependence (physical and psychological dependence).
10. Acute morphine poisoning: The characteristic triad of symptoms are respiratory depression, pinpoint pupils and coma.

Codeine: Codeine has analgesic and cough-suppressant effects; Compared to morphine:

a. It is less potent as an analgesic.
b. It has a less respiratory depressant effect.
c. It has a selective cough suppressant effect (antitussive).
d. It potentiates analgesic effect of aspirin and paracetamol. Codeine is used for the relief of moderate pain.
e. The main side effects are constipation and sedation.

Pethidine (Meperidine): The adverse effects are similar to those of morphine. It can cause tremors, hallucinations, muscle cramps and rarely convulsions due to its metabolite, norpethidine. Tolerance and physical and psychological dependence can also develop with pethidine.

Tramadol is a synthetic codeine derivative with weak agonistic activity at μ-receptors. It also inhibits the reuptake of noradrenaline and 5-hydroxytryptamine (5-HT). (Less than with equianalgesic doses of morphine).

Fentanyl is a synthetic opioid with a potent μ-agonistic effect (100 times more powerful than morphine as an analgesic). Pharmacological actions are similar to morphine.

Methadone is a synthetic opioid with an agonistic effect at μ-receptors; it has a long duration of action. Pharmacological actions are similar to morphine.

Dextropropoxyphene: It is structurally similar to methadone. The side effects are nausea, constipation, sedation, abdominal pain, etc.

Opioid Antagonists: Naloxone & Naltrexone: Competitively reverse the effects of both natural and synthetic opioids. **Uses of naloxone:** The primary therapeutic use of naloxone is for treating morphine and other opioid poisoning. In the treatment of opioid overdosage, intravenous naloxone rapidly reverses the respiratory depression induced by opioids (except buprenorphine, which it causes partial reversal of respiratory depression).

Psychopharmacology

Antipsychotic drugs are also known **as neuroleptic drugs or anti-schizophrenic drugs. Neuroleptic drugs are mainly used in schizophrenia, acute mania and other acute psychotic states.**

Antipsychotic drugs: Chlorpromazine, trifluoperazine, thioridazine, fluphenazine, Haloperidol, Clozapine, risperidone, olanzapine, aripiprazole,

- **Chlorpromazine** is the prototype drug.

Pharmacological actions of chlorpromazine:

1. **Central nervous system:** In patients with schizophrenia, chlorpromazine:

- Reduces agitation and aggressiveness.
- Suppresses hallucinations and delusions.

2. **Endocrine:** Prolactin secretion is controlled by a prolactin-releasing factor (PRF) and prolactin-inhibitory factor (PIF). PIF itself is dopamine; hence the blockade of DA-receptors in the pituitary may cause increased production of prolactin leading to galactorrhoea, amenorrhoea and infertility in females; gynecomastia in males.

Adverse effects of antipsychotics

- Parkinsonism.
- Acute dystonias: Uncontrolled muscular movements involving the face, tongue, neck,
- Akathisia: Feeling of restlessness (state of agitation).
- Tardive dyskinesia (Tardive: late occurring): It is characterized by involuntary movements of the mouth, tongue and upper limbs. It develops in about 20% of patients after months or years of antipsychotic treatment.
- Weight gain is common with clozapine and olanzapine.
- Endocrine side effects are due to increased prolactin levels resulting in amenorrhoea, galactorrhoea and infertility in females; gynaecomastia in males.
- Hypersensitivity.

ANTIANXIETY AGENTS

- **Benzodiazepines:** Benzodiazepines are the preferred anxiolytic drugs. Chlordiazepoxide, diazepam, lorazepam, oxazepam, alprazolam, etc., are used as anxiolytic agents.
- **Buspirone:** Buspirone is a partial agonist of the 5-HT_{1A} -receptor and causes the selective anxiolytic effect. It has no sedative, anticonvulsant or muscle-relaxant effects. It is mainly used in the treatment of generalized anxiety states.
- **β-Blockers:** Propranolol and other nonselective **β**-blockers are used mainly to reduce anxiety symptoms, such as tachycardia, palpitation, tremor, sweating, etc.
- **Selective serotonin reuptake inhibitors (SSRIs) and serotonin and noradrenaline reuptake inhibitors (venlafaxine) are the preferred agents for most** anxiety disorders except acute anxiety. The response is delayed.

ANTIDEPRESSANTS

- Tricyclic antidepressants: Amitriptyline, Nortriptyline, Imipramine, Doxepin.
- Selective serotonin (5-HT) reuptake inhibitors (SSRIs): Fluoxetine, citalopram, sertraline, and paroxetine.
- Atypical antidepressants: Trazodone, duloxetine, mirtazapine, venlafaxine.

Uses of Antidepressants

- **Depression**
- **Panic disorders**
- **Obsessive-compulsive disorders (OCD):** Clomipramine and fluvoxamine are highly effective.
- **Nocturnal enuresis (incontinence):** Imipramine is effective.
- **Prophylaxis of migraine:** Amitriptyline is effective.
- **Chronic pain, including neuralgias:** TCAs are effective in trigeminal, herpetic, post-herpetic neuralgias, etc.

Tricyclic Antidepressants:

Adverse effects and contraindications of tricyclic antidepressants

- 'Atropine-like' side effects: Dryness of mouth, blurring of vision, constipation, urinary retention, etc.
- **α_1**-adrenergic blocking effects: Postural hypotension, tachycardia, cardiac arrhythmias, etc.
- H_1 -blocking effects: Sedation and confusion.
- Other effects include increased appetite and weight gain; convulsions may be precipitated (seizure threshold is lowered).

Tricyclic antidepressants are **contraindicated** in patients with glaucoma, epilepsy, ischaemic heart disease and enlarged prostate.

Bipolar disorder: (manic-depressive illness) is a psychiatric disorder in which depression alternates with mania. Mania is an affective disorder that manifests as elation (Joy), agitation, hyperactivity, uncontrolled thought and speech.

Drugs used in bipolar disorder are lithium, carbamazepine, sodium valproate, olanzapine, risperidone, haloperidol, etc.

Lithium was the first drug used for the treatment of mania. Lithium has a low therapeutic index; hence therapeutic drug monitoring (TDM) is essential for optimal therapy. Estimation of salivary concentration can be used for non-invasive monitoring of lithium.

Adverse effects

1. GIT: Nausea, vomiting and diarrhoea.
2. CNS: Tremor, ataxia, drowsiness, headache, muscular weakness and slurred speech.
3. Renal: Polyuria, polydipsia due to inhibition of ADH action.
4. Goitre with hypothyroidism and weight gain.
5. Acute lithium toxicity manifests as confusion, convulsions, cardiac arrhythmias, coma and death.

Uses

It is used as a prophylactic agent for bipolar disorder. It decreases the frequency and severity of both manic and depressive attacks; hence it is called a mood stabilizer. Lithium has a slow onset of action and is not useful for acute mania. Lithium is also helpful in the prophylaxis of unipolar depression.


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Drugs used in the treatment of Gastrointestinal disease

- Antacids and antacid/alginate combinations
- Drugs that inhibit gastric acid secretion:
  - Proton pump inhibitors
  - H_2-receptor antagonists
- Drugs that act on gastric motility (Nausea and vomiting)
- Irritable bowel syndrome
- Drugs used in non-specific diarrhoea
- Drugs used in Constipation
- Drugs adversely affecting gastrointestinal function

Antacids and antacid/alginate preparations

Antacids are weak alkalis, so they partly neutralize free acid in the stomach. They may also stimulate mucosal repair mechanisms around ulcers, possibly through local prostaglandin release.

Adverse effects

Antacids that contain aluminium tend to cause constipation. Those containing magnesium have the opposite effect. Absorbable antacids should not be administered in the long term. Antacids with a high sodium content should be avoided in patients with **impaired cardiac function or chronic liver disease.**

Proton pump inhibitors (PPIs): Omeprazole, Lansoprazole, Pantoprazole, Rabeprazole, and Esomeprazole

The proton pump is an enzyme (H^+/K^+-ATPase) that actively secretes **hydrogen ions** into the gastric lumen. It is the final common pathway in the process of **acid secretion**. Blocking this enzyme **suppresses gastric acid secretion** to any stimulus, including food.

PPI has been shown to protect against ulcer development in patients taking long-term NSAIDs (‘**gastroprotection**’).

Adverse effects

These are mild and infrequent. Diarrhea, skin rash, and headache have all been reported.

Drug interactions

Omeprazole **reduces the clearance and prolongs the elimination of** diazepam, phenytoin, and warfarin by inhibiting their **hepatic metabolism**.

Drugs used in the treatment of peptic ulcer

H_2-receptor antagonists

The two most used are **ranitidine and cimetidine.**

H_2-receptor antagonists are competitive antagonists for histamine at the H_2-receptor, resulting in **reduced acid secretion** by the parietal cells, especially at night and in the fasting state. They are less effective in reducing food-stimulated acid secretion.

Adverse effects

These are rare and are usually minor. Cimetidine is weakly **anti-androgenic** in humans and may cause **impotence or gynecomastia**. Cimetidine and ranitidine may cause reversible mental confusion, particularly in frail (weak) elderly patients. Some potentially severe cardiac dysrhythmia has occurred following intravenous injections of H_2-receptor antagonists.

Sucralfate **(sucrose aluminium octa sulphate)**

Mechanism

The mechanism of ulcer healing by sucralfate is unknown. It may act by **coating ulcer bases or stimulating local prostaglandin release.** It does **NOT** directly affect acid secretion. However, it suppresses *H. pylori* infection and thus reduces acid hypersecretion. It suppresses *H. pylori* by interfering with the ability of the organism to bind to the mucosal epithelial cells.

Sucralfate is **indicated** for treating Duodenal ulcer (DU) and benign Gastric ulcer (GU).

Pharmacokinetics: Sucralfate acts **locally;** only small amounts of aluminium are absorbed.

Adverse effects: Constipation.

Prostaglandin E Analog

Medication: **Misoprostol**

Pharmacological Action

Prostaglandin E analog acts as an endogenous prostaglandin in the GI tract to decrease acid secretion, increase the secretion of **bicarbonate and protective mucus**, and promote vasodilation to maintain sub-mucosal blood flow. These actions all serve to **prevent gastric ulcers.**

Therapeutic Uses

-Prostaglandin E analog is used in patients taking long-term **NSAIDs to prevent gastric ulcers.**

-Prostaglandin E analog is used in pregnancy to **induce labor by causing cervical ripening.**

Adverse effects: Diarrhea and abdominal pain, nausea, vomiting.

Contraindications/Precautions: <u>Pregnancy Risk Category X</u>

Drugs used in the treatment of vomiting

Anticholinergic drugs: **Hyoscine**

Anticholinergic drugs compete with acetylcholine at muscarinic receptors in the gut and **CNS** and have anti-spasmodic action in the gut wall. They **may be successful in motion sickness** because of their **central action.**

Adverse effects

Adverse effects include drowsiness and typical anticholinergic effects of **dry mouth, blurred vision, and difficulty in micturition (urination).**

Antihistamines: Promethazine

Antihistamines are competitive histamine antagonists at H1-receptors, acting mainly on the vomiting center rather than the chemoreceptor trigger zone. They have **weak** anticholinergic effects.

Adverse effects

Adverse effects include drowsiness, insomnia, and euphoria.

Clinical use

Antihistamines are used in **motion sickness or vestibular disorders.** They are widely used to treat allergic rhinitis and other allergic reactions.

Dopamine antagonists: phenothiazines: chlorpromazine, prochlorperazine

Mechanism

They act mainly on the **chemoreceptor trigger zone** with **dopamine receptor antagonist** properties and anticholinergic properties.

Adverse effects

Prolonged use may produce **Parkinsonian-type tremors or other dyskinesia.**

Dopamine antagonist: metoclopramide

Metoclopramide is a **central dopamine receptor antagonist** that blocks stimuli to the chemoreceptor trigger zone.

Adverse effects

Metoclopramide may cause acute extrapyramidal reactions. These are mainly a hazard when **metoclopramide treats children and young adults.** They can be treated with an intravenous **anticholinergic agent, such as benztropine.**

Metoclopramide raises serum prolactin levels and may cause **gynaecomastia** through its antidopaminergic effects.

Dopamine antagonist: Domperidone

Domperidone is a **dopamine antagonist**, effective at the **chemoreceptor trigger zone.**

Adverse effects

Domperidone is **less likely** to cause extrapyramidal reactions than metoclopramide. It raises **prolactin levels and may produce cardiac dysrhythmias following rapid intravenous injection.**

Serotonin antagonists: Ondansetron

Ondansetron is a **selective antagonist of serotonin at 5-HT3 receptors**. The mode of action in controlling nausea and vomiting is unclear, but it **has both CNS and peripheral actions.**

Adverse effects

Ondansetron causes constipation and headache; flushing may occur.

Clinical use and dose

Ondansetron is indicated for treating **nausea and vomiting associated with cytotoxic therapy or radiotherapy**. The dose and rate of administration depend on the severity of the problem and the chemotherapy used.

Irritable bowel syndrome IBS

This common condition is the most frequent cause of chronic, recurrent abdominal pain. It may also cause bloating and upset bowel habits (diarrhea, constipation, or both). **There is a relationship between psychological stress and symptoms in some patients.**
Management consists of non-pharmacological treatment (lifestyle advice) with combinations of antispasmodics and titrated doses of antimotility drugs or laxatives with tricyclics/SSRIs employed as a second line to provide visceral analgesia.

- **Mebeverine** is an antispasmodic agent without significant anticholinergic effects. It helps relieve symptoms in some patients.

- Enteric-coated capsules of **peppermint oil** help relieve gut spasms in some patients.

- **Tricyclic antidepressant** drugs can be effective if second-line therapy is required.

- There is also some evidence supporting the use of the selective serotonin reuptake inhibitor (SSRI) **citalopram for this indication.**

Drugs used in non-specific diarrhea

Codeine phosphate

This is useful for the symptomatic control of diarrhea. **It raises intracolonic pressure and sphincter tone**. It should not be given to patients with colonic diverticular disease. It should be used cautiously in patients with inflammatory bowel disease and only under the careful supervision of a gastroenterologist.

Diphenoxylate

This is an opiate derivative. **It is combined with atropine in the preparation of Lomotil.**

Loperamide

Loperamide is a synthetic opiate **with some anticholinergic activity.** It may cause dizziness or dryness of the mouth. The usual dose is 2 mg tds or qds.

Constipation

There is a wide variation in normal bowel habits. It is, therefore, important to establish exactly what the patient means by constipation before embarking (start) on treatment and to exclude any other underlying medical conditions or drug treatments that may be contributing to the problem.

Constipation treatment

Faecal bulk

These consist of non-absorbable polysaccharides, as in **bran and ispaghula.** They are generally effective in simple constipation, mainly where dietary fiber intake is poor. They are the agents of choice where treatment is likely to be prolonged but may be slow to act, requiring a degree of persistence (insistence). **They increase fecal mass and stimulate peristalsis but require adequate fluid intake.**

Osmotic laxatives

These agents retain and draw water into the bowel. **They increase fecal bulk and moisten feces**, e.g., non-absorbable disaccharide **lactulose and magnesium salts**.

Stimulant laxatives

These agents **stimulate intestinal motility,** e.g., **senna and bisacodyl**. Avoid if an intestinal obstruction is suspected. Prolonged use may lead to bowel hypotonicity and exacerbate chronic constipation.

Stool softeners

Stool softeners **increase the water content of stool** to make it easier to pass, e.g., **docusate sodium** in either a liquid or capsule form. **Glycerin suppositories are** also helpful in promoting bowel movement.

Drugs adversely affect gastrointestinal function.
Virtually any drug may cause nausea, vomiting, or diarrhea; a detailed drug history is essential in patients with such complaints.

Antibiotic-related diarrhea is usually attributed to an **alteration** in the intracolonic bacterial **flora**, but antibiotic-associated colitis or **pseudomembranous colitis can occur**. This results from the proliferation of ***Clostridium difficile*** in the bowel and the secretion of an endotoxin.

Prevention is achieved by the limited, wise use of antibiotics and good hygiene in clinical areas. Treatment depends on the prescription of an antibiotic, which is poorly absorbed when given orally. Two suitable agents are **vancomycin and metronidazole.**


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Pharmacology

Dentistry College

Diabetes & Insulin, Oral Anti Diabetic, Parathyroid Hormone

Calicum , Vit D ,Biphosphonate

TIKRIT UNIVERSITY

(2024-2025)

Year 3

Assistant lecturer

FARAH MOHAMMED NAJEEB

Diabetes & Insulin

Diabetes mellitus (DM) is a clinical syndrome characterized by **hyperglycemia** due to absolute or relative **deficiency of insulin**. Lack of insulin affects the metabolism of carbohydrates, protein, and fat.

Type 1 diabetes mellitus: It appears when more than 90% of β cells of the pancreas are destroyed by an autoimmune process. The aetiology is **immunological or idiopathic**.

Type 2 diabetes mellitus: Genetic influence is much more powerful in type-2 DM. It is the commonest form of diabetes. Overeating, obesity, underactivity, and aging are the main risk factors. **Type-2 DM is associated with increased hepatic production of glucose and resistance of target tissues to the action of insulin.**

Insulin

Insulin was discovered by Banting and Best. Insulin is synthesized by the β cells of pancreatic islets from a single-chain polypeptide precursor called **preproinsulin**, which is converted to **proinsulin**. Insulin is formed by the removal of the C-peptide from proinsulin by proteolysis.

Site of administration

Insulin is usually administered subcutaneously in the abdomen, buttock, anterior thigh, or dorsal arm.

Mechanism of action of insulin

Insulin binds to specific receptors (receptor tyrosine kinase) present on the cell membrane.

www.youtube.com/watch?v=OYH1deu7-4E

Pharmacokinetics

Insulin is destroyed by **proteolytic enzymes** in the gut and, hence, is **not effective orally**. Insulin is administered usually by subcutaneous (s.c.) route; but in emergencies, regular (soluble) insulin is given by i.v. route. After i.v. injection, soluble insulin is rapidly metabolized by the liver and kidney with a half-life of **about 6 min**.

Insulin Preparations

1. **Conventional insulin preparations:**
- Bovine (beef) insulin.
- Porcine (pig) insulin.
2. **Monocomponent insulins:**

Conventional insulin preparations obtained from beef and pork pancreas (bovine and porcine insulin, respectively) are immunogenic. These preparations contain pancreatic proteins, proinsulin, insulin fragments, etc.

3. **Human insulins:** They are produced by recombinant DNA technology using E.coli or yeast.

Insulin therapy

Insulin is the main drug for all patients with type-1 DM and for patients with type-2 DM who are not controlled by diet and oral antidiabetic drugs. The main goal of insulin therapy is to maintain the fasting blood glucose concentration between 90 and 120 mg/dL and a postprandial glucose level below 150 mg/dL.

Concentration of insulin

Insulin preparations are available in a concentration of 100 or 40 U/mL. Regular insulin is also available in 500 U/mL. Insulin dosage is measured in **units (U)**. All insulin preparations are administered by **s.c. route. Regular insulin** can be given **by i.v.** route in diabetic **ketoacidosis** to obtain a rapid effect.

NOTE: **N**eutral **insulin / S**oluble **insulin** is a type of short-acting **insulin**.

Insulin administration

- Insulin syringes and needles.
- Pen devices: They are convenient to carry; a pre-set amount is delivered subcutaneously.
- Insulin pumps are available for continuous subcutaneous insulin infusion.

Indications for insulin

1. Type 1 diabetes mellitus.
2. Diabetic ketoacidosis.
3. **Diabetes during pregnancy.**
4. The stress of surgery, infections, and trauma (temporarily to tide over trauma, infection, surgery, etc.). (**The stress response to surgery** consists of two main components: neuroendocrine–metabolic and inflammatory–immune. After surgery, there is a state of hyper-catabolism, which produces readily useable metabolic energy sources.
5. Patients with type 2 DM are unresponsive to oral antidiabetic drugs.

Complications of insulin therapy

1. **Hypoglycaemia** is the most common and dangerous complication. Prolonged hypoglycaemia may cause permanent brain damage.

Symptoms of hypoglycaemia are:

a. **Sweating, tremor, palpitation, anxiety and tachycardia.**
b. Neuroglycopenic symptoms like **headache, blurred vision, confusion, loss of fine motor skills, and abnormal behaviour**.
2. **Allergic reactions**
3. **Lipodystrophy** (either atrophy or hypertrophy) may occur at the injection site.
4. **Insulin resistance.**
5. **Oedema** due to salt and water retention.

Drug interactions

1. **Beta Blockers** with Insulin.
2. **Salicylates**: Salicylates exert a hypoglycaemic effect by increasing the sensitivity of pancreatic Beta-cells to glucose and potentiating insulin secretion.

Diabetic ketoacidosis (DKA) (Is a medical emergency).

DKA develops when the body doesn't have enough insulin to allow blood sugar into your cells for use as energy. Without enough insulin, the body begins to break down fat as fuel. This causes a build-up of acids in the bloodstream called ketones. If it's left untreated, the buildup can lead to diabetic ketoacidosis.

Diabetic ketoacidosis is a **complication of Type 1 diabetes mellitus**. It is **very rare in Type 2 DM**. The common **precipitating factors** are infection, trauma, severe stress, etc. The clinical features are anorexia, nausea, vomiting, polyuria, abdominal pain, hypotension, tachycardia, hyperventilation, altered consciousness, or coma in untreated cases. It is treated with **regular insulin (i.v.); correcting fluid and electrolyte imbalance is essential**.

Oral Antidiabetic Drugs

1. **Sulfonylureas.**
a. **First generation**: Tolbutamide, Chlorpropamide.
b. **Second generation**: Glibenclamide, glipizide, gliclazide, glimepiride.
2. **Biguanides**: Metformin.
3. **Meglitinide analogue**: Repaglinide.
4. **D-phenylalanine derivative**: Nateglinide.
5. **Thiazolidinediones:** Pioglitazone.
6. **Glucosidase inhibitors**: Acarbose, miglitol.

Newer antidiabetic agents

GLP-1receptor-agonist: Exenatide.
DPP-4 inhibitors: Sitagliptin.

Note: Sulfonylureas, Meglitinides, and D-phenylalanine derivatives promote insulin secretion.

Sulfonylureas

Use

Sulfonylureas are useful in patients with type 2 diabetes mellitus.

Mechanism of action

Sulfonylureas stimulate insulin secretion from β-cells of the pancreas.

Adverse effects

1.Hypoglycaemia.
2.GI disturbances like nausea, vomiting, diarrhoea, and flatulence.
3.Weight gain is due to the stimulation of appetite.
4.Allergic reactions.
5.Teratogenicity: Sulfonylureas **are not safe during pregnancy.**
6.Chlorpropamide has **disulfiram-like action** and, hence, produces **intolerance to alcohol.**

Biguanides: **Metformin** is the only biguanide used clinically.
Mechanism of action: It is as follows.

1. Inhibit hepatic gluconeogenesis.
2. Inhibit alimentary absorption of glucose.
3. Increase peripheral utilization of glucose and decrease lipogenesis in adipose tissue.

Adverse effects: Metallic taste, anorexia, nausea, vomiting, diarrhoea, and skin rashes. Lactic acidosis is the most serious complication but is rare with metformin. Prolonged use can cause vitamin B_{12} deficiency due to malabsorption. Metformin usually does not cause hypoglycaemia, even in large doses.
Use: Metformin is a commonly used first-line drug for treating type-II DM. It can be used alone or in combination with other antidiabetic agents.

Lactic acidosis occurs when lactic acid production exceeds lactic acid clearance. The increase in lactate production is usually caused by impaired tissue oxygenation, either from decreased oxygen delivery or a defect in mitochondrial oxygen utilization.

Meglitinide Analogue (Repaglinide) and D-Phenylalanine Derivative (Nateglinide)

Repaglinide and Nateglinide are structurally **unrelated** to sulfonylureas, but **their mechanism of action is similar to sulfonylureas**.

They are used only in type-II DM to control postprandial hyperglycaemia.

The main side effects of repaglinide are weight gain and hypoglycaemia, but the episodes are less frequent; meglitinide causes nausea and flu-like symptoms.

Thiazolidinediones (Thia zolidine diones):
They increase the sensitivity of peripheral tissues to insulin.

Pioglitazone reduces serum triglyceride and increases HDL levels.

Adverse effects

Nausea, vomiting, anaemia, weight gain, oedema, and precipitation of heart failure in patients with low cardiac reserve; rarely have hepatotoxicity been reported.

Uses

Pioglitazone is used alone or in combination with sulfonylureas/metformin in patients with type-2 diabetes mellitus.

Liraglutide (*Saxenda)* **is a GLP-1 analog** used in the management of type 2 diabetes mellitus and the prevention of cardiovascular complications associated with diabetes.

DPP-4 (dipeptidyl peptidase–4) inhibitors, e.g., sitagliptin, saxagliptin: They **increase insulin secretion, suppress glucagon release, slow gastric emptying,** and improve control of postprandial hyperglycemia. They are administered orally in patients with type 2 diabetes mellitus. Allergic reactions can occur with sitagliptin. Respiratory and urinary tract infections may be seen with saxagliptin.

α-**Glucosidase** Inhibitors: These drugs should be given just before food. **Acarbose, miglitol, and Voglibose reduce the intestinal absorption of carbohydrates by inhibiting the enzyme α-glucosidase in the small intestine and reducing postprandial hyperglycaemia**. They are mainly **used** in obese type-2 DM patients. **Side effects** are primarily to the GI tract: flatulence, fullness, and diarrhoea.

Newer Drugs

GLP-1 receptor agonists, e.g., exenatide: Glucagon-like peptide-1 (GLP-1) is released from the gut after meals. It **stimulates insulin secretion**, **suppresses glucagon release,** and **slows gastric emptying**.

Agents affecting calcium balance

Calcium

- About 99% of calcium of our body is in bone and teeth.
- Calcium metabolism is chiefly regulated by three hormones: parathormone (PTH), vitamin D (di-hydro-chole-calciferol) and calcitonin.
- Parathormone plays a central role in regulating calcium homeostasis.
- Calcium metabolism is also intimately (closely) connected with phosphorus and magnesium metabolism.
- The normal serum calcium level is 9–11 mg/dL.

Preparations of calcium

Oral & Parenteral

Therapeutic uses of calcium salts

1. **To correct calcium deficiency**:

a. In growing children, pregnant and lactating women.
b. In dietary deficiency.
c. In postmenopausal osteoporosis.
d. In rickets and osteomalacia, along with vitamin D.
e. In long-term corticosteroid therapy along with vitamin D.
f. After the removal of the parathyroid tumour.

2. Intravenous calcium gluconate (10%) in tetany.

3. Calcium carbonate is used as an antacid.

Parathyroid Hormone (PTH)

Parathormone is a polypeptide hormone that is synthesized by the chief cells of the parathyroid gland.

Hypoparathyroidism (Deficiency of Parathyroid Hormone).

Serum calcium levels are decreased.

Treatment:

1. Emergency treatment of acute attack (hypoparathyroidism tetany)
2. Treatment of chronic hypoparathyroidism

Hyperparathyroidism

Hyperparathyroidism is characterized by increased levels of parathormone, often due to a parathyroid tumour. There is hypercalcaemia and hypercalciuria. Some cases of hyperparathyroidism can be treated with **cinacalcet**, which acts on the parathyroid gland to decrease PTH secretion.

Treatment

Surgical removal of the parathyroid tumour.

Calcitonin

The main actions of calcitonin are to lower serum calcium and phosphate by direct action on bone and kidney. Calcitonin secretion is stimulated when the serum calcium level becomes high and vice versa.

Therapeutic uses

1. **In hypercalcaemic states** (e.g., associated with neoplasia).
2. **In Paget's disease of bone**: Chronic use of calcitonin relieves pain and reduces some of the neurological complications, but bisphosphonates are the treatment of choice.
3. **In postmenopausal osteoporosis and corticosteroid-induced osteoporosis**: Salmon calcitonin is used as a nasal spray along with calcium and vitamin D supplements.

Adverse effects

Nausea, vomiting, flushing and pain at the site of injection.

Vitamin D

- Vitamin D is a fat-soluble vitamin. It is a prohormone, which is converted in the body into a number of biologically active metabolites that function as true hormones.
- Vitamin D, together with PTH, plays a central role in the maintenance of plasma calcium and bone formation.
- Vitamin D is found in fish liver oils and dairy products and is also synthesized in the skin upon exposure to sunlight.

Actions of vitamin D

- Vitamin D deficiency causes rickets in children and osteomalacia in adults.
- Hypervitaminosis D may occur due to acute large doses or long-term use of vitamin D.
- The signs and symptoms of hypercalcaemia are nausea, weakness, fatigue, and polyuria. If hypercalcaemia persists, calcium salts are deposited in the kidney, resulting in renal failure and renal stones. Treatment includes immediate stoppage of vitamin D, a low-calcium diet, intravenous hydration, and administration of glucocorticoids.

Therapeutic uses of vitamin D

1. Prevention and treatment of nutritional rickets and osteomalacia.
2. **Renal rickets**: It is associated with chronic renal failure.
3. In **hypoparathyroidism**, there is hypocalcaemia and hyper phosphataemia.
4. Administration of vitamin D with calcium in **senile or postmenopausal osteoporosis** improves calcium balance and may reduce the risk of fractures.

Bisphosphonate

Bisphosphonates are analogues of pyrophosphate. They are etidronate (oral, i.v.), **alendronate** (oral), pamidronate (i.v. infusion), zoledronate (i.v. infusion), risedronate (oral), etc.

Uses

1. **Paget's disease of bone. (**deterioration of bone tissue**)**
2. **For prevention and treatment of postmenopausal osteoporosis.**
3. To prevent **corticosteroid-induced osteoporosis** along with oral calcium carbonate.
4. **Hypercalcaemia of malignancy.**

Adverse effects

They include nausea, vomiting, diarrhoea, heartburn, oesophagitis, peptic ulcer, fever, myalgia hypocalcaemia, headache, and skin rashes. **Oral bisphosphonates should be taken with plenty of water, and the patient should remain upright for at least 30 minutes to prevent oesophagitis.** Flu-like symptoms can occur on parenteral administration. Rarely, Bisphosphonates can cause osteonecrosis of the jaw.


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Autacoids

The word ‘autacoids’ comes from the Greek words: *autos* (self) and *Akos* (medicinal agent). Autacoids are **produced by cells and act locally.** Hence, they are also called ‘**local hormones**. Various autacoids are **histamine, serotonin (5-HT), prostaglandins (PGs), leukotrienes, angiotensin, kinins and platelet activating factor (PAF).**

HISTAMINE AND ANTIHISTAMINES

Histamine is a biogenic amine present in many animal and plant tissues. It is also present in venoms and stinging secretions. Histamine is mainly present in storing granules of mast cells in tissues like skin, lungs, liver, gastric mucosa, placenta, etc. **It is one of the mediators involved in inflammatory and hypersensitivity reactions.**

Mechanism of action and effects of histamine

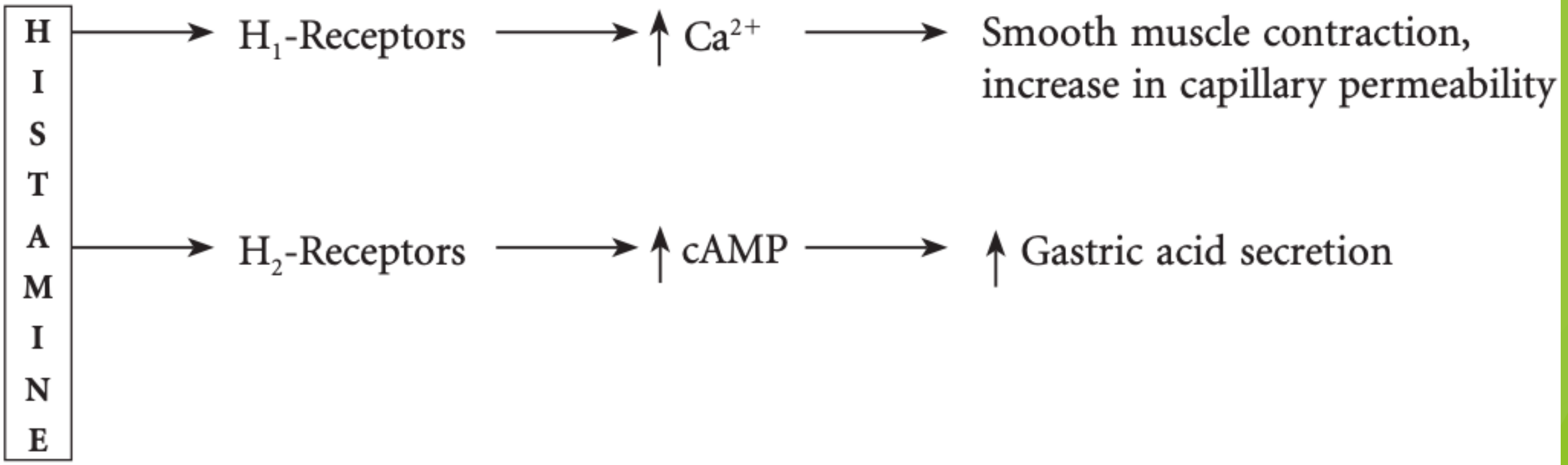
Histamine exerts its effects by binding to histamine (H) receptors.

Histamine liberators

Many agents release histamine from **mast cells**.

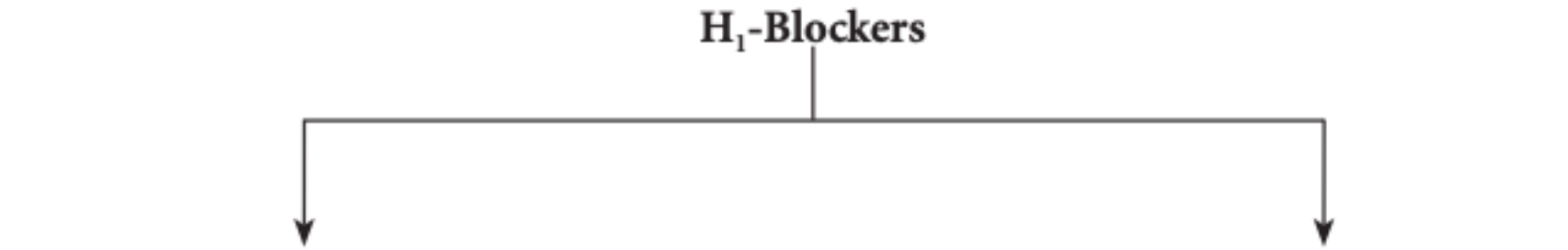
Uses

Histamine has **no proper clinical use.**


HISTAMINE
H1-Receptors
↑ Ca2+
Smooth muscle contraction,
increase in capillary permeability
H2-Receptors
↑ cAMP
↑ Gastric acid secretion

H_1-receptor Antagonists (H_1-blockers, Antihistamines)

Classification



First-generation agents

- Diphenhydramine
- Dimenhydrinate
- Promethazine
- Cinnarizine
- Cyclizine, meclizine
- Hydroxyzine
- Pheniramine
- Chlorpheniramine maleate
- Cyproheptadine
- Clemastine
- Triprolidine

Second-generation agents

- Cetirizine
- Levocetirizine
- Azelastine
- Mizolastine
- Loratadine
- Desloratadine
- Fexofenadine
- Ebastine

Mechanism of action of H_1-blockers

H_1-antihistamines antagonize the effects of histamine by competitively blocking H_1-receptors (competitive antagonism).

First-generation H_1-blockers:

They are conventional antihistamines.

Pharmacological actions

1.H-blockers cause central nervous system **(CNS)** depression—sedation, and drowsiness. Certain antihistamines have **antiemetic** and **antiparkinsonian effects.**

2.They have **antiallergic action**.

3.They have **anticholinergic actions.**

Adverse effects

1.The common adverse effects are sedation, drowsiness, lack of concentration, headache, fatigue, weakness, lassitude, incoordination, etc. Hence, H-antihistamines should be avoided while driving or operating machinery.

2. Gastrointestinal side effects are nausea, vomiting, loss of appetite, and epigastric discomfort.

3. Anticholinergic side effects include dry mouth, blurred vision, constipation, and urinary retention.

Uses

1. **Allergic diseases:** H -antihistamines are used to prevent and treat symptoms of **allergic reactions**, for example, pruritus, urticaria, dermatitis, rhinitis, and conjunctivitis.

2. Common cold: They produce symptomatic relief by sedative and anticholinergic actions.

3. Preanesthetic medication: Promethazine is used for its sedative and anticholinergic effects.

4. As antiemetic: Promethazine, diphenhydramine, dimenhydrinate, etc., are valid for **preventing** motion sickness because of their anticholinergic action. These drugs are helpful in morning sickness and drug-induced and postoperative vomiting. Promethazine is used to control vomiting due to cancer chemotherapy and radiation therapy.

5. Parkinsonism: The imbalance between dopamine and acetylcholine in the basal ganglia produces parkinsonism. Promethazine, diphenhydramine, and orphenadrine control tremors, rigidity, and sialorrhoea of parkinsonism due to **their anticholinergic and sedative properties**. Promethazine and diphenhydramine are also helpful for treating extrapyramidal side effects caused by phenothiazines or metoclopramide.

6. Cinnarizine, dimenhydrinate, and meclizine effectively control **vertigo** in Meniere's disease and other types of vertigo.

7. Sedative and hypnotic: H-antihistamines (e.g., promethazine and diphenhydramine) induce sleep, especially in children during minor surgical procedures.

Second-generation H_1-blockers

Cetirizine, loratadine, azelastine, and fexofenadine are highly selective for H-receptors and have the following properties.

1. **Have no** anticholinergic effects.

2. **Lack** antiemetic effect.

3. **Do not** cross the blood–brain barrier (BBB), hence causing minimal/no drowsiness.

4. **Do not** impair psychomotor performance.

5. They Are relatively **expensive.**

Cetirizine

Cetirizine is one of the commonly used **second-generation antihistamines.** In addition to H –the blocking effect, it can **inhibit histamine release.** It causes minimal/no drowsiness. It is not metabolized in the body. Incidence of cardiac arrhythmias is rare with this drug.

Uses

Second-generation H -blockers are used in various allergic disorders—rhinitis, dermatitis, conjunctivitis, urticaria, eczema, and drug and food allergies.

H_3 receptor antagonist

H_3 receptor antagonist is a classification of drugs used to block the action of **histamine at the H_3 receptor.**

Unlike the H_1 and H_2 receptors which have **primarily peripheral actions** but cause **sedation if blocked in the brain**, H_3 receptors are found mainly in the brain. They are inhibitory autoreceptors located on histaminergic nerve terminals, which modulate histamine release.

H_3 antagonists have **stimulant** and **nootropic** effects and are being researched as potential drugs for treating neurodegenerative conditions such as **Alzheimer's.**
Examples of selective H_3 antagonists include **betahistine** and **pitolisant**.

Betahistine

It is a **potent antagonist** of the histamine H_3 receptor and a **weak** agonist of the histamine H_1 receptor.

It is a histamine analog used orally to treat vertigo in Meniere's disease. It probably acts by **improving blood flow in the inner ear.** The side effects are nausea, vomiting, headache, and pruritus**.** It should be **avoided** in patients with **asthma and peptic ulcer.**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Prostaglandins

- **Arachidonic acid** is the precursor for the biosynthesis of **all PGs.**
- The enzyme involved in the formation of PGs from arachidonic acid is **cyclooxygenase (COX).**
- **There are TWO** forms of COX, COX-1, and COX-2.
- COX-1 participates in various **physiological functions** such as protecting **gastric mucosa**, **homeostasis**, **regulation of cell division, etc.**
- COX-2 is induced during **inflammation** by cytokines and endotoxins.

Pharmacological ACTIONS and uses of PG:

1.Misoprostol prevents nonsteroidal anti-inflammatory drug (NSAID)-induced ulcers.

2. Cardiovascular system:

- Thromboxane $_{A2}$ (TX_{A2}) is a vasoconstrictor.
- Alprostadil is used to maintain the **patency (the condition of being open, expanded, or unobstructed) of the ductus arteriosus** before surgery.

3. Platelets: PG inhibits platelet aggregation. Hence, it is used during hemodialysis to prevent platelet aggregation.

4. Eye: PG has been found to decrease intraocular tension. e.g., **Latanoprost and Travoprost** are used in glaucoma.

5. Uterus: PG contract the pregnant uterus. PGs are mainly used in mid-trimester abortion and missed abortions. Other uses include induction of labour.

6. Male reproductive system: Alprostadil is useful for treating erectile dysfunction.

Adverse effects

They are nausea, vomiting, diarrhoea, fever, flushing, hypotension, and backache. Injections are painful.

Nonsteroidal anti-Inflammatory Drugs Classification:

1. Nonselective cyclooxygenase (COX) inhibitors
   a. Salicylates: **Aspirin.**
   b. Propionic acid derivatives: **Ibuprofen & Naproxen.**
   c. Acetic acid derivatives: **Diclofenac.**
   d. Fenamic acid derivatives: **Mefenamic acid.**
   e. Pyrrole derivatives: **Ketorolac.**
   f. Oxicam derivatives: **Piroxicam & Tenoxicam.**
   g. Indole derivatives: **Indomethacin.**
2. Preferential COX-2 inhibitors: **Nimesulide & Meloxicam.**
3. Highly selective COX-2 inhibitors: **Celecoxib & Etoricoxib.**
4. Analgesic antipyretics with poor anti-inflammatory effect: **Paracetamol & Nefopam.**

Mechanism of action

- PGs have an important role in many tissues.
- COX-2 is **induced during inflammation** by cytokines and endotoxins and is responsible for producing **prostanoid mediators of inflammation**.
- **Aspirin** and most **nonsteroidal anti-inflammatory drugs (NSAIDs)** inhibit COX-1 and COX-2, **decreasing** prostaglandin and thromboxane synthesis.
- The anti-inflammatory effect of NSAIDs is mainly due to the **inhibition of COX2**.
- Aspirin causes **irreversible inhibition of COX**. The rest of the NSAIDs cause **reversible inhibition of the enzyme.**

Pharmacological actions of aspirin and other NSAIDs

- **Analgesic effect:** NSAIDs are mainly used for relieving musculoskeletal pain, dysmenorrhea, and pain associated with inflammation or tissue damage.
- **Antipyretic effect:** The thermoregulatory center is **situated in the hypothalamus**. Fever occurs when there is a **disturbance** in the hypothalamic thermostat.
- NSAIDs **reset** the hypothalamic thermostat and reduce the elevated body temperature during fever. They promote heat loss by causing cutaneous vasodilatation and sweating. The antipyretic effect is mainly due to the inhibition of PGs in the hypothalamus.
- **Anti-inflammatory effect:** Is seen at high doses (aspirin: 4–6 g/day in divided doses). These drugs produce **only symptomatic relief.** They suppress signs and symptoms of inflammation such as pain, tenderness, swelling, vasodilatation, and leukocyte infiltration **but do not affect** the progression of underlying disease.

- **Antiplatelet (antithrombotic) effect:** Aspirin in **low doses** (50–325 mg/day) irreversibly inhibits platelet TX_{A2} synthesis and produces an antiplatelet effect, which lasts for 8–10 days, i.e., the lifetime of platelets. Aspirin in **high doses** (2–3 g/day) inhibits both PG and TX synthesis; hence the **beneficial effect of PG is lost**. Aspirin should be withdrawn 1 week before elective surgery because of **the risk of bleeding.**

- **Gastrointestinal tract** (**GIT):** Aspirin irritates the gastric mucosa and produces nausea, vomiting, and dyspepsia. Aspirin also stimulates the chemoreceptor trigger zone (CTZ) and produces vomiting.

- **Cardiovascular system (CVS):** Prolonged use of aspirin and other NSAIDs causes **sodium and water retention**. They may precipitate congestive cardiac failure (CCF) in patients with low cardiac reserve. They may also decrease the effect of **antihypertensive drugs.**

Adverse effects.

1. GIT: Nausea, vomiting, dyspepsia, epigastric pain, acute gastritis, ulceration, and GI bleeding. **The ulcerogenic** effect can be prevented/minimized by taking: NSAIDs after food, proton pump inhibitors/H_2-blockers/Misoprostol with NSAIDs, buffered aspirin (preparation of aspirin with antacid), and selective COX-2 inhibitors.

2.Hypersensitivity: It is relatively more common with **aspirin**.
The manifestations are skin rashes, urticaria, rhinitis, and **bronchospasm**. **Bronchospasm (aspirin-induced asthma)** is due to the increased **production of leukotrienes**. The incidence of hypersensitivity is high in patients with **asthma, nasal polyps, recurrent rhinitis, or urticaria**. **Therefore, aspirin should be avoided in such patients.**

3. In people with glucose-6-phosphate dehydrogenase (G6PD), administration of salicylates may cause **hemolytic anemia.**

4. Prolonged use of salicylates interferes with the action of vitamin K in the liver & decreases synthesis of clotting factors (can be treated by administration of vitamin K).

5. Reye's syndrome: The use of salicylates in children with viral infection may cause hepatic damage with fatty infiltration and encephalopathy (Reye's syndrome). Hence, salicylates **are contraindicated in children with viral infections.**

Note: **Reye's (Reye) syndrome** is a rare but serious condition that causes swelling in the liver and brain.

6. Pregnancy: These drugs inhibit PG synthesis, thereby **delaying the onset of labour** and **increasing the chances of postpartum hemorrhage**. In the newborn, inhibition of PG synthesis results in **premature closure of the ductus arteriosus.**

7. Analgesic nephropathy: Slowly progressive renal failure may occur on **chronic use of high doses of NSAIDs.** Renal failure is usually reversible on stoppage of therapy, but rarely, NSAIDs may cause irreversible renal damage.

Table 7.4 Differences Between Nonselective COX and Selective COX-2 Inhibitors

Nonselective COX Inhibitors	Selective COX-2 Inhibitors
Analgesic effect +	Analgesic effect +
Antipyretic effect +	Antipyretic effect +
Antiinflammatory effect +	Antiinflammatory effect +
Antiplatelet effect +	No antiplatelet effect
GI side effects are marked + +	GI side effects are less (less ulcerogenic potential)
Renal toxicity + (sodium and water retention)	Renal toxicity +

+: present; ++: effect is more.

- **Paracetamol** is effective by oral and parenteral routes. It is well absorbed, widely distributed all over the body, and metabolized **in the liver**. **Paracetamol** has a central analgesic effect that is mediated by activating **descending serotonergic pathways.** Debate exists about its primary site of **action**, which may be the inhibition of prostaglandin (PG) synthesis or through an active metabolite influencing cannabinoid receptors.
- **Uses As** Antipyretic, Analgesic. It is the preferred analgesic and antipyretic in patients with peptic ulcer, hemophilia, bronchial asthma, and children.
- **Adverse effects:** Side effects are rare and occasionally cause skin rashes and nausea. Hepatotoxicity & Nephrotoxicity is commonly seen in **chronic use.**

Table 7.5 Differences Between Aspirin and Paracetamol

Aspirin	Paracetamol
1. It is a salicylate derivative	1. It is a *para*-aminophenol derivative
2. It has analgesic, antipyretic and potent antiinflammatory effects	2. It has potent antipyretic and analgesic effects with poor antiinflammatory activity
3. It causes GI irritation (nausea, vomiting, peptic ulcer and bleeding)	3. It usually does not produce gastric irritation
4. In large doses, it produces acid–base and electrolyte imbalance	4. It does not produce acid–base and electrolyte imbalance
5. It has antiplatelet action	5. It has no antiplatelet action
6. It has no specific antidote	6. *N*-acetylcysteine is the antidote
7. It is contraindicated in peptic ulcer, people with bleeding tendency, bronchial asthma and in children with viral infection	7. Paracetamol is the preferred analgesic and antipyretic in patients having peptic ulcer, bronchial asthma and in children


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Pharmacology

Respiratory System

Dentistry College

TIKRIT UNIVERSITY

(2024-2025)

Year 3

Assistant lecturer

FARAH MOHAMMED NAJEEB

Respiratory System

Drugs Used in **Treatment of Cough (**Cough is a protective reflex intended **to remove irritants and accumulated secretions** from the respiratory passages).

Drugs used in the symptomatic treatment of cough are:

1. **Antitussives (cough center suppressants):** Codeine, dextromethorphan, antihistamines.
2. **Pharyngeal demulcents** Lozenges, liquorice.
3. **Expectorants:** Potassium iodide, guaiphenesin, ammonium chloride.
4. **Mucolytics** Bromhexine, acetylcysteine.

Cough may be:

1. Productive cough: Helps to clear the airway. Suppression of productive cough is harmful as it may lead to infections. Treatment includes **antibiotics for infection, expectorants, and mucolytics for cough.**

2. Nonproductive cough: It is useless and should be suppressed.

Antitussives

They inhibit the cough reflex by suppressing the cough center in the medulla. They are used for the **symptomatic treatment** of **dry, unproductive cough**. Antitussives should be avoided in children below the age of 1 year.

1.Codeine: Has **cough center suppressant** effect. It causes mild CNS depression; hence drowsiness can occur. Causes constipation by decreasing intestinal movements.

2.Dextromethorphan: It is a **centrally acting** antitussive agent. It **has no** analgesic properties and does not cause constipation or addiction.

3.Antihistamines: Diphenhydramine, chlorpheniramine, promethazine, etc., are useful in cough due to their sedative, antiallergic, and anticholinergic actions. They produce symptomatic relief in colds and coughs associated with allergic conditions of the respiratory tract.

Pharyngeal Demulcents

Syrups, lozenges, or liquorice (la.kush.rush) may be used when a cough arises due to irritation above the larynx. They increase salivation and produce a protective, soothing effect on the inflamed mucosa.

Expectorants (Mucokinetics)

They increase the volume of bronchial secretion and reduce the viscosity of the sputum; hence, the cough becomes less tiring and productive. They include iodides, chlorides, bicarbonates, acetates, volatile oils, etc. These drugs are useful in the **treatment of chronic cough.**

Mucolytics

These agents break the thick tenacious (sticky) sputum and lower the viscosity of sputum so that the sputum comes out easily with less effort. E.g., **Bromhexine:** The side effects are rhinorrhea and lacrimation.

Acetylcysteine and carbocisteine: The side effects are nausea, vomiting, and bronchospasm.

Drugs used in the treatment of bronchial asthma

In bronchial asthma, airflow is impaired due to bronchial smooth muscle contraction (bronchospasm), swelling of bronchial mucosa (mucosal edema), and increased bronchial mucus secretion. Several factors may precipitate attacks of asthma in susceptible individuals. They include allergy, infection, and psychological factors. Airway obstruction in asthma is mainly due to the release of mediators from sensitized mast cells in the lungs. They are histamine, serotonin (5-HT), PGs, leukotrienes, etc.

Bronchial asthma may be either episodic or chronic.

Acute asthma is characterized by an episode of dyspnoea associated with expiratory wheezing.

Chronic asthma: Continuous wheezing and breathlessness on exertion; cough and mucoid sputum with recurrent respiratory infection are common.

Status asthmaticus (severe acute asthma):

When an asthma attack is prolonged with severe intractable wheezing, it is known as severe acute asthma.

Classification of anti-asthmatic drugs

1. **Bronchodilators:**
- **Selective β_2-adrenergic agonists:** Salbutamol & terbutaline (short-acting).
- **Nonselective:** Adrenaline.
- **Methylxanthines:** Theophylline, aminophylline.
- **Anticholinergics:** Ipratropium bromide.

2. **Leukotriene receptor antagonists:** Montelukast.

3. **Mast cell stabilizers:** Sodium cromoglycate, ketotifen.

4. **Glucocorticoids:**
- **Inhaled glucocorticoids:** Beclomethasone, fluticasone.
- **Systemic glucocorticoids:** Hydrocortisone, prednisolone, methylprednisolone.

- **Adrenaline** (non-selective sympathomimetic): Bronchodilatation is useful in an **acute asthma attack**. Its use has declined because of its **dangerous cardiac side effects.**

- **Selective β_2 -adrenergic agonists** are the first-line drugs for bronchial asthma. They are well tolerated when inhaled. High doses may cause **tremors, tachycardia, palpitation, hypokalemia, and rarely cardiac arrhythmias**.

- **Methylxanthines** in asthma have markedly diminished because of their **narrow margin of safety**. They can cause **tachycardia, palpitation, hypotension (due to vasodilatation), and sometimes sudden death due to cardiac arrhythmias.**

Anticholinergics

- **Ipratropium** bromide and tiotropium bromide are atropine substitutes.
- They selectively block the effects of acetylcholine in the bronchial smooth muscles and **cause bronchodilatation**.
- They have a **slow onset of action and are less effective than sympathomimetic drugs in bronchial asthma**.
- These anticholinergics are the preferred bronchodilators in COPD and can also be used in bronchial asthma.
- They are administered by the inhalational route.
- Combined use of ipratropium with β_2- adrenergic agonists produce greater and more prolonged bronchodilatation. Hence, they are used in acute severe asthma.

Leukotriene Antagonists

- These drugs competitively block the effects of leukotrienes on **bronchial smooth muscle**.
- They produce **bronchodilatation**, suppress **bronchial inflammation,** and decrease **hyperreactivity**.
- They are well absorbed after oral administration, highly bound to plasma proteins, and metabolized extensively in the liver.
- They are effective for the **prophylactic treatment of mild asthma.**
- They are well tolerated and produce fewer adverse effects, such as headaches and skin rashes.

Mast Cell Stabilizers

- **Sodium cromoglycate** and **ketotifen** are mast cell stabilizers. **They are not bronchodilators.** They inhibit the release of various mediators: histamine, LTs, PGs, etc., by stabilizing the mast cell membrane. They also **reduce bronchial hyperreactivity to some extent, but antigen–antibody reaction** (AG–AB reaction) is not affected.
- Sodium cromoglycate is not effective orally as it is poorly absorbed from the gut. **In bronchial asthma, sodium cromoglycate is given by inhalation.**
- Sodium cromoglycate is **a prophylactic agent** to prevent **bronchospasm induced by allergens and irritants**. It can also be used in **allergic conjunctivitis, allergic rhinitis, and allergic dermatitis.**
- **Ketotifen:** The mechanism of action is similar to sodium cromoglycate and has an additional **H_1-blocking effect**. It is orally effective but has a slow onset of action.

Glucocorticoids

- **Systemic Glucocorticoid:** Hydrocortisone, prednisolone, methylprednisolone, and others.

- **Inhalational Glucocorticoid:** Beclomethasone, fluticasone, etc.

- **Glucocorticoids have antiallergic, anti-inflammatory, and immunosuppressant effects. They s**uppress the inflammatory response to AG–AB reaction, Decrease mucosal edema, and Reduce bronchial hyperactivity.

- Glucocorticoids do not have a direct **bronchodilating effect but potentiate the effects of β-adrenergic agonists.**
- Inhaled glucocorticoids such as beclomethasone, budesonide, and fluticasone are **prophylactic agents in bronchial asthma.**

Glucocorticoids

- The common side effects **are hoarseness of voice, dysphonia, and oropharyngeal candidiasis**. These can be reduced by using a spacer, rinsing the mouth after each dose, and treating effectively with a topical antifungal agent such as nystatin.

- A combination of a long-acting β-agonist with a steroid is available, e.g.,. fluticasone + salmeterol; budesonide + formoterol. They have synergistic action; used in bronchial asthma and COPD.

- Systemic glucocorticoids are used in acute severe asthma and chronic severe asthma.
- **Long-term use of systemic steroids produces severe side effects such as gastric irritation, $Na,^{+}$ and water retention, hypertension, muscle weakness, osteoporosis, hypothalamo–pituitary–adrenal axis (HPA axis) suppression, etc.**

Treatment of Acute Severe Asthma (Status Asthmaticus)

- **Oxygen** inhalation.
- Nebulized **β2 -adrenergic agonist** (salbutamol /terbutaline) + **anticholinergic agent** (Ipratropium bromide).
- Systemic **glucocorticoids**: Intravenous hydrocortisone or oral prednisolone, depending on the patient's condition.
- **Intravenous fluids** to correct dehydration.
- **Potassium supplements**: To correct **hypokalaemia** produced by repeated doses of salbutamol/ terbutaline.
- **Sodium bicarbonate** to treat acidosis.
- **Antibiotics** to treat the infection.


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Pharmacology

Chemotherapy I

Dentistry College

TIKRIT UNIVERSITY

(2024-2025)

Year 3

Assistant lecturer

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1

General considerations

- **Chemotherapy** treats infectious diseases or malignancies with drugs that preferentially destroy microorganisms or cancer cells with **minimal damage** to **host tissues**. The infection may be due to bacteria, viruses, fungi, protozoa, or helminths.

- **Antibiotics** are chemical substances obtained from microorganisms that kill or suppress the growth of other organisms **at a very low concentration.**

- **Bactericidal agents kill** or **destroy** microorganisms, e.g., penicillins, cephalosporins, aminoglycosides, etc.

- **Bacteriostatic agents inhibit the growth and multiplication** of microorganisms, e.g., sulphonamides, tetracyclines, chloramphenicol, erythromycin, etc.

- **At high concentrations**, some of the '**static**' drugs may produce a '**cidal**' effect; for example, **chloramphenicol is a bacteriostatic drug, but it may be bactericidal** against Haemophilus influenzae, Neisseria meningitis, and Streptococcus pneumoniae.

- **Antimicrobial agents** (AMAs) are synthetic and naturally obtained drugs that act against microorganisms.

- **Minimum inhibitory concentration** (MIC) is the minimum concentration of an antimicrobial agent that prevents the visible growth of a microorganism.

Classification of Antimicrobial Agents

According to their type of action:

a. Bactericidal agents;

Penicillins, Cephalosporins, Aminoglycosides, Fluoroquinolones, Rifampin, and Metronidazole.

b. Bacteriostatic agents:

Tetracyclines, Chloramphenicol, Sulphonamides, Dapsone, Erythromycin, Clindamycin.

Resistance to Antimicrobial Agents

Resistance is defined as the **unresponsiveness** of a microorganism to an **Anti Microbial Agent** (AMA). The resistance may be **natural or acquired**.

The **natural resistance** is genetically determined, e.g., normally, gram-negative bacilli are not affected by penicillin G.

In **acquired resistance**, microbes that initially respond to an AMA later develop resistance to the same AMA by mutation or gene transfer, e.g., **Gonococcal Resistance** to penicillins.

The transfer of genes for drug resistance occurs by the following mechanisms:

Cross-resistance

Organisms that develop resistance to an antimicrobial agent may **also show resistance** to other chemically related AMAs. The cross-resistance among AMAs could either be one-way or two-way.

-Cross-resistance among **tetracyclines** and **sulphonamides** is usually ‘two-way.’

-The ‘one-way’ resistance is seen between neomycin and streptomycin. Neomycin-resistant organisms are resistant to streptomycin, **BUT** streptomycin-resistant organisms may be **sensitive to neomycin.**

Prevention of the development of resistance to antimicrobial agents is done by:

1.Selecting the **Right antimicrobial** agent.
2.Giving the **Right dose** of the AMA for the proper duration.
3.The proper combination of AMAs, e.g., in tuberculosis (TB), and multidrug therapy (MDT), is used to prevent the development of resistance to antitubercular drugs by mycobacteria.

Superinfection (Suprainfection)

- It is defined as the appearance of a new infection due to antimicrobial therapy.
- The causative organism of superinfection should be different from that of the primary disease.
- Most of the AMAs, especially broad-spectrum antibiotics (tetracyclines, chloramphenicol), clindamycin, ampicillin, etc., alter the normal bacterial flora, impairing the host defense mechanism. Hence, pathogenic organisms invade the host, multiply and produce superinfection.
- **The causative organism may be fungi or bacteria.**

Table 11.1 Microorganisms Causing Superinfection and Its Treatment

Manifestations	Microorganisms	Treatment
Diarrhoea, oral thrush	*Candida albicans*	Nystatin, clotrimazole, fluconazole
Pseudomembranous enterocolitis	*Clostridium difficile*	Metronidazole, vancomycin
Urinary tract infection	*Escherichia coli, Proteus, Pseudo-monas*	Ciprofloxacin, gentamicin, car-benicillin

Factors predisposing to superinfection

Superinfection is common in **immunocompromised conditions**, such as **diabetes**, **malignancy,** and **AIDS**, and during prolonged **corticosteroid therapy**.

It can be minimized by:

- Using specific antimicrobial agents,
- Avoiding unnecessary use of AMAs.
- Use of probiotics, e.g., Lactobacillus.

Chemoprophylaxis

- Chemoprophylaxis is the administration of antimicrobial agents **to prevent infection or disease development** in persons who are already infected.

- The ideal time to initiate therapy is before the organism enters the body or at least before developing signs and symptoms of the disease.

Indications for chemoprophylaxis

- To prevent endocarditis in patients with valvular lesions before undergoing **surgical procedures.**
- To protect healthy persons: Chloroquine /mefloquine is used for **malaria chemoprophylaxis** for those traveling to the malaria-endemic area.
- To prevent infection in patients undergoing **organ transplantation.**
- To prevent opportunistic infections in **immunocompromised patients.**
- Before surgical procedures: Antimicrobial agents are administered to all patients before **major dental surgical procedures or implantation of prosthetic devices** and in patients with diabetes **or who are on prolonged corticosteroids** to **prevent** wound infection after surgery.
- To prevent infection in patients **with burns**.

- **Empirical therapy**: It is the use of antimicrobial agents **before the identification** of causative organism or availability of susceptibility test results, e.g., a combination of amoxicillin, cefotaxime, and vancomycin are used as empirical therapy **for suspected bacterial meningitis** (before test results are available) to cover possible organisms likely to cause meningitis.

- **Definitive therapy** involves antimicrobial agent use after identification/susceptibility tests of the causative organism responsible for the disease.

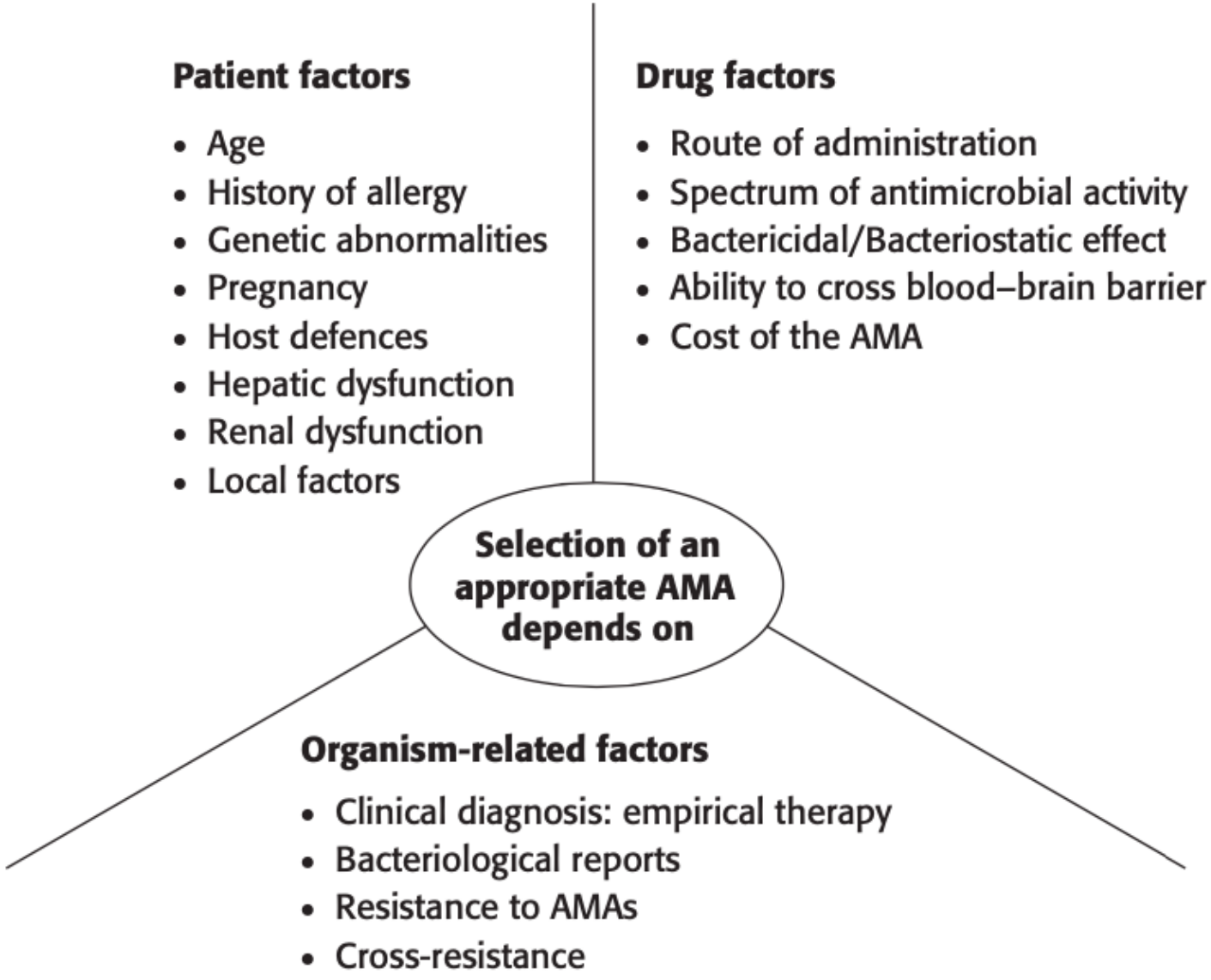

Fig. 11.3 Factors affecting selection of an antimicrobial agent.

1- Sulphonamides

- The sulphonamides were the first effective antimicrobial agents used to treat bacterial infections in man.

- **Mechanism of action** Para-aminobenzoic acid **(PABA)** is a precursor of **folic acid**, which is essential for **the growth and multiplication of many bacteria.**
- Sulphonamides, structurally similar to PABA, competitively inhibit folate synthetase enzyme and prevent folic acid formation, producing the **bacteriostatic effect**.

Adverse effects

1. It may cause **crystalluria, haematuria,** or even obstruction to the urinary tract.
2. **Hypersensitivity** reactions include skin rashes and itching. **Stevens–Johnson syndrome** is the most severe type of hypersensitivity reaction characterized by **fever, erythema multiforme, and ulceration of mucous membranes.**
3. In patients with G6PD deficiency, sulphonamides may cause acute **hemolytic anemia**.
4. The use of sulphonamides in **neonates**, especially premature babies, may cause **displacement of bilirubin from plasma proteins**. The free bilirubin can cross the blood–brain barrier and get deposited in the basal ganglia resulting in **kernicterus (kernic-terus).**

Drug interactions

Sulphonamides **potentiate** the effect of **phenytoin, methotrexate, oral anticoagulants, and oral hypoglycemic agents (sulfonylureas)** by **inhibiting** their metabolism. **(Enzyme Inhibitor)**

Therapeutic uses (Indications)

- Sulphonamides alone **are rarely used** now for systemic infections. They are used in combination with other antimicrobial agents.
- Sulphacetamide is used topically for the treatment of **ophthalmic infections.**

Cotrimoxazole

Cotrimoxazole is a World Health Organization (WHO)-approved–fixed-dose combination of sulphamethoxazole and trimethoprim in a ratio of 5:1.

The combination produces a **supra-additive effect**. An optimum synergistic effect is seen in blood and tissues at a concentration ratio of 20:1 (Sulphamethoxazole to Trimethoprim).

The advantages of this combination are:

1. **Individually, both are bacteriostatic, but the combination has a cidal effect.**
2. The chances of the development of bacterial resistance are **also significantly reduced.**

Adverse effects

- The common adverse effects are skin rashes and gastrointestinal (GI) disturbances. The GI symptoms include nausea.
- Stevens–Johnson syndrome is rare.
- **Cotrimoxazole is contraindicated in pregnancy.**

Therapeutic uses (Indications)

1.Urinary tract infection.
2.Bacterial respiratory tract infections.
3.Bacterial diarrhea.
4.Typhoid fever.

2- Quinolones

- The first quinolone, **Nalidixic acid**, is a urinary antiseptic.
- It is useful in treating **uncomplicated UTIs** due to gram-negative bacteria and diarrhoea due to Shigella or Salmonella.
- The most common adverse effects are related to the **GI tract, central nervous system (CNS), and skin.**

Fluoroquinolones

Fluoroquinolones are synthetic fluorinated analogues of nalidixic acid. The important fluoroquinolones are **Norfloxacin, Ciprofloxacin, Pefloxacin, Ofloxacin, Levofloxacin, Gemifloxacin and Moxifloxacin.**

Fluoroquinolones inhibit **bacterial DNA** gyrase resulting in the inhibition of DNA synthesis, which is responsible for their activity against gram-negative bacteria. They also inhibit **topoisomerase (topoisomerase)**, contributing to their activity against gram-positive bacteria.

Antibacterial spectrum

Ciprofloxacin **is the prototype drug**. Ciprofloxacin is highly effective against aerobic gram-negative organisms, e.g., E. coli, Klebsiella, Salmonella, and Shigella. It has activity against S. aureus, Pseudomonas aeruginosa, and Mycobacterium tuberculosis.

Newer fluoroquinolones like **levofloxacin, Gemifloxacin, moxifloxacin, etc., have more significant activity against streptococci and some activity against anaerobes.**

Adverse effects

- The common adverse effects are related to the GI tract, e.g., **nausea, vomiting, and abdominal discomfort**.
- CNS effects include **headache, dizziness, insomnia, confusion, hallucinations, and convulsions**.
- **Hypersensitivity** reactions include skin rashes and **photosensitivity.**
- **Tendon rupture** can occur, especially in athletes.
- Fluoroquinolones are **contraindicated in pregnancy**.
- Fluoroquinolones have caused **cartilage damage** in animals, hence should be **avoided in young children**.

Drug interactions

- Ciprofloxacin increases the plasma concentration of theophylline, warfarin, etc., **by inhibiting their metabolism**.
- Nonsteroidal anti-inflammatory drugs **(NSAIDs)** may potentiate the **CNS side effects of fluoroquinolones, confusion, irritability,** and rarely convulsions may occur.
- Like tetracyclines, the absorption of fluoroquinolones **is reduced by antacids, ferrous salts, and sucralfate.**

Uses of fluoroquinolones (Indications)

1.Urinary tract infections:
2.Bacterial diarrhoea: caused by E. coli, Shigella, Salmonella, etc.
3.Typhoid fever.
4.Sexually transmitted diseases: Fluoroquinolones are effective for gonococcal infections.
5.Respiratory infections.
6.Others: Skin, soft tissue, and bone infection.


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Beta-lactam antibiotics

Beta-lactam antibiotics include Penicillins, Cephalosporins, Carbapenems (Meropenem), and Monobactams (Aztreonam).

Penicillin was the first antibiotic developed and used clinically. It was discovered accidentally by Alexander Fleming.

Mechanism of action

Beta-lactam antibiotics produce a **bactericidal effect** by **inhibiting cell wall synthesis** in susceptible bacteria.

Mechanism of bacterial resistance to penicillins

Bacteria develop resistance:

- Producing β-lactamases, which **destroy** the β-lactam ring, e.g., S. aureus, E. coli, gonococci, H. influenzae, etc.
- Due to **altered (penicillin-binding proteins) PBPs**, which have less affinity for β-lactams, e.g., S. pneumoniae
- Due to **decreased ability** of the drug to penetrate its site of action.

Adverse reactions of penicillin

- Penicillins are **relatively safe**.
- They may cause hypersensitivity reactions, such as skin rashes, urticaria, fever, dermatitis, bronchospasm, angioedema, joint pain, serum sickness, or anaphylactic reaction.
- The **major manifestations of anaphylactic shock** are severe **hypotension**, **bronchospasm,** and **laryngeal oedema**.
- It is **NOT** a dose-related adverse drug reaction and can occur with any dosage form of penicillin.
- **Cross-reactivity** can occur among penicillins and also among β-lactams antibiotics.

Treatment of anaphylactic shock

1. Inj. **adrenaline** intramuscularly.
2. Inj. **hydrocortisone** 200 mg intravenously.
3. Inj. **diphenhydramine** 50–100 mg intramuscularly or intravenously.

Precautions

1. In patients with a history of **asthma, allergic rhinitis, hay fever**, etc., there is an increased risk of penicillin allergy; hence it should be avoided.

2.Inj. adrenaline and hydrocortisone should be kept ready before injecting penicillin to treat the anaphylactic reaction.

Therapeutic uses of penicillin

1.In dentistry: Penicillins are used in **Vincent's angina** (a painful ulcerative condition of the inside of the mouth or the gums, associated with trench mouth)., **necrotizing gingivitis**, **periodontal infections**, etc., either alone **or with metronidazole**.

2.Pneumococcal infections.

3.Streptococcal infections.

4.Meningococcal meningitis.

5.Gonococcal infections.

6.Syphilis.

7.Diphtheria.

Prophylactic uses of penicillins.

1. **Rheumatic fever**, for rheumatic fever prophylaxis. Patients allergic to penicillin are treated with erythromycin or sulphadiazine.

2. **Bacterial endocarditis**: Patients with valvular lesions are at high risk of developing infective endocarditis; hence they should receive chemoprophylactic agents before dental or surgical procedures to prevent bacteraemia.

Therapeutic uses of Amoxicillin (Aminopenicillins)

1.In dentistry: Amoxicillin is used alone or with metronidazole in acute necrotizing ulcerative gingivitis, dentoalveolar abscess, osteomyelitis of the mandible, etc.
2.Upper respiratory infections.
3.Subacute bacterial endocarditis.
4.Urinary tract infections.
5.Meningitis.
6.Bacillary dysentery
7.Typhoid fever.

Adverse effects: The adverse effects of ampicillin are similar to those of penicillin, but **skin rashes and diarrhoea are more common.**

Antipseudomonal penicillins

They are Carbenicillin, Ticarcillin, Mezlocillin and Piperacillin

Uses: Serious infections such as bacteremias, pneumonia, UTIs, burns, etc.
P. aeruginosa and Proteus are more effectively treated with piperacillin than carbenicillin.

Adverse effects are similar to penicillin.

β-Lactamase Inhibitors

They are **clavulanic acid, sulbactam and tazobactam**. Beta-lactamase inhibitors bind to β-lactamases and inactivate them. **Co-administration** of these drugs with β-lactams increases the activity of β-lactams by preventing them from enzymatic destruction. They are clavulanic acid, sulbactam and tazobactam.

Clavulanic acid

It competitively and irreversibly inhibits β-lactamases. After binding to the enzyme, clavulanic acid gets inactivated; hence it is called a ‘suicide’ inhibitor.

Cephalosporins

Cephalosporins are β-lactam antibiotics. The mechanism of action and resistance are **similar to penicillins.** Like penicillins, cephalosporins also **inhibit the synthesis of the bacterial cell wall and produce a bactericidal effect.** Cephalosporins have been divided into **FIVE (5) generations** based on their general features and antibacterial activity**.**

Cephalosporins

1. **First generation**: Cephalothin, Cefazolin, Cephalexin.
2. **Second generation**: Cefamandole, Cefoxitin, Cefuroxime.
3. **Third generation**: Cefotaxime, Ceftriaxone, Cefoperazone, Ceftazidime.
4. **Fourth generation:** Cefepime.
5. **Fifth generation**: Ceftaroline.

Table 11.9 Antibacterial Spectrum, Pharmacokinetics and Uses of Cephalosporins

Cephalosporins	First Generation	Second Generation	Third Generation	Fourth Generation
1. Drugs	Cephalexin (O) Cefadroxil (O) Cefazolin (i.m., i.v.) Cephradine (O, i.m., i.v.) Cephalothin (i.m.)	Cefaclor (O) Cefuroxime axetil (O) Cefuroxime (i.m., i.v.) Cefoxitin (i.m., i.v.) Cefotetan (i.m.) Cefprozil (O)	Cefixime (O) Cefpodoxime proxetil (O) Ceftriaxone (i.m., i.v.) Cefotaxime (i.m., i.v.) Cefoperazone (i.m., i.v.) Ceftazidime (i.m., i.v.) Ceftizoxime (i.m., i.v.) Cefdinir (O) Ceftibuten (O)	Cefepime (i.v.) Cefpirome (i.m., i.v.)
2. Antibacterial spectrum: • Against gram-positive organism (except enterococci and MRSA)	+++	++	+	+
• Against gram-negative organisms	+ (*E. coli, K. pneumoniae*)	++ (*E. coli, K. pneumoniae, Proteus, H. influenzae*)	+++	+++
• Anaerobes	Effective against oral cavity anaerobes except *Bacteroides fragilis*	Effective against anaerobes including *B. fragilis* (cefotetan, cefoxitin)	Effective against anaerobes including *B. fragilis* (cefoperazone, ceftizoxime)	Not effective against *B. fragilis.*
• Against *Pseudomonas*	Not effective	Not effective	Effective (cefoperazone, ceftazidime)	Effective
• Against *Salmonella*	Not effective	Not effective	Effective (ceftriaxone, cefoperazone)	

Table 11.9 Contd...

Cephalosporins	First Generation	Second Generation	Third Generation	Fourth Generation
3. β-lactamase enzyme	Among the first-generation agents, cefazolin is highly susceptible to staphylococcal β-lactamases	Cefoxitin and cefuroxime are resistant to β-lactamases produced by gram-negative organism	Most of them are resistant to most of the β-lactamases (except cefoperazone) produced by gram-negative organisms	Same as third generation
4. Blood–brain barrier (BBB)	–	Some of the second-generation drugs (cefuroxime) cross the BBB	Cefotaxime, ceftriaxone cross BBB and reach high concentration in CSF	Cross BBB

5. Uses	1. In dentistry: Cephalexin and cefadroxil can be used orally for odontogenic infections (but not as first-line drugs). Cephalexin/cefadroxil/cefazolin can be used for prophylaxis of bacterial endocarditis before dental procedures as alternatives to amoxicillin. 2. Skin and soft-tissue infections due to streptococci and *Staphylococcus aureus* 3. Surgical prophylaxis: Cefazolin is preferred because of its longer duration of action	1. In dentistry: Cefaclor or cefuroxime axetil are useful for orodental infections. 2. Respiratory tract infections: otitis media and sinusitis, oral cefuroxime axetil can be used 3. Cefoxitin and cefotetan are preferred for mixed (gram-negative bacteria and anaerobes) intra-abdominal and pelvic infections	Third-generation cephalosporins alone or with aminoglycosides are used in severe gram-negative infections 1. Pyelonephritis caused by gram-negative organisms: ceftriaxone 2. Community-acquired pneumonia : Ceftriaxone, cefotaxime 3. Gonorrhoea: Ceftriaxone is the drug of choice. 4. Typhoid fever: Ceftriaxone and cefoperazone are very effective for the treatment of multidrug-resistant *Salmonella* infections 5. Meningitis caused by *Haemophilus influenzae:* Inj. cefotaxime and ceftriaxone are the preferred drugs 6. Mixed aerobic and anaerobic infections seen in patients with malignancy 7. Septicaemia caused by gram-negative infections 8. Nosocomial infection: Third-generation drugs are useful	Same as third-generation. They are reserve drugs for hospital-acquired resistant infections

+: less active; ++: moderately active; +++: highly active

Adverse effects

1.Hypersensitivity: The most common adverse effects are allergic reactions.
2.Gastrointestinal disturbances, mainly diarrhoea, vomiting, and anorexia, can also occur.
3.Pain at the site of i.m. injection, mainly with cephalothin. Intravenous cephalosporins can cause thrombophlebitis.
4.Nephrotoxicity may occur. Co-administration of cephalothin and gentamicin increases nephrotoxicity.
5.Alcohol intolerance (a disulfiram-like reaction- nausea, vomiting, flushing, dizziness, throbbing headache, chest, and abdominal discomfort**)** has been reported with cefotetan and cefoperazone.
6.Severe bleeding can occur due to hypoprothrombinaemia (a response to vitamin K therapy), thrombocytopenia, and platelet dysfunction.

Aminoglycosides

They include Streptomycin, Gentamicin, Tobramycin, Amikacin, Kanamycin, Sisomicin, Neomycin, Framycetin, And Netilmicin.

Common properties of aminoglycosides:

- They are administered by the **parenteral** route (i.m./i.v.) for systemic effect.
- They are **not metabolized** in the body.
- They are **excreted** unchanged in the urine.
- They have **bactericidal** action against gram-negative aerobes and are more active at alkaline pH.
- They exhibit **ototoxicity** and **nephrotoxicity**.
- They exhibit partial **cross-resistance** among them.

Mechanism of action

Aminoglycosides are **bactericidal agents: that inhibit protein synthesis.**

- **Aminoglycosides exhibit** A concentration-dependent killing effect; the higher the plasma concentration, the more bacteria are killed rapidly.
- In a post-antibiotic effect, the bactericidal effect is present even when serum concentration falls below minimum inhibitory concentration (MIC). Therefore, a once-daily dosing regimen is effective.

Uses

1. Streptomycin: is one of the first-line drugs for **tuberculosis (TB)** and is used in combination with other antitubercular drugs. The other uses include brucellosis.

2. Gentamicin: is the most used aminoglycoside antibiotic. It is available for parenteral and topical administration.

Therapeutic uses of gentamicin

A. In dentistry: **Prophylaxis of bacterial endocarditis:** Gentamicin can be combined with amoxicillin/ vancomycin for endocarditis prophylaxis in high-risk patients before dental or other surgical procedures.

B. Severe infections: Urinary tract infection with pyelonephritis, Pneumonia, Meningitis, Osteomyelitis, and Septicemia.

3. Neomycin: is highly nephrotoxic, hence **NEVER** used for systemic effect. It is used only for local effects for wounds, ulcers, burns, and eye and ear infections. It can be used orally to prepare the bowel before abdominal surgery and in hepatic encephalopathy.

4. Framycetin (Soframycin): Like neomycin, Framycetin is also highly nephrotoxic, hence not used for systemic administration. Framycetin is widely used topically for skin, eye, and ear infections.

5. Amikacin: It is useful for treating nosocomial gram-negative infections and tuberculosis.

6. Tobramycin: It is superior to gentamicin against P. aeruginosa and useful in treating serious infection by this organism.

7. Netilmicin: It is resistant to aminoglycoside-inactivating enzymes and effective against most gentamicin-resistant bacteria.


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Pharmacology

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Year 3

Assistant lecturer

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Tetracyclines & **chloramphenicol**

Tetracyclines and **chloramphenicol** are broad-spectrum antibiotics. They are called so because of their effectiveness against a wide range of microorganisms, such as gram-positive and gram-negative cocci.

1- Tetracyclines :Mechanism of action: Inhibit bacterial protein synthesis (**Bacteriostatic**)

Adverse effects

1. Gastrointestinal: Nausea, vomiting, epigastric distress, abdominal discomfort, and diarrhoea.

2. Effects on bones and teeth: Tetracyclines have **calcium-chelating properties, forming tetracycline–calcium orthophosphate complex deposited in growing bone and teeth**. The use of tetracyclines in children and during pregnancy can cause **permanent brownish discolouration of the deciduous (Milky, primary) teeth due to the deposition of the chelate in the teeth.** The incidence of **hepatotoxicity is more in pregnant women**. Therefore, tetracyclines **are contraindicated** during pregnancy for both foetus and the mother. **It is also contraindicated in children up to the age of 8 years.**

3. Phototoxicity: Sunburn-like reaction.

4. **Superinfection:** It is common with older tetracyclines because of their incomplete absorption in the gut; they cause alteration of the gut flora. **Superinfection occurs** with organisms resistant to tetracyclines like Candida, etc. Pseudomembranous colitis caused by C. difficile is a serious complication. **It is characterised by** severe diarrhoea, fever, abdominal pain, and stool mixed with blood and mucus, treated with oral metronidazole.
5. **Hepatotoxicity:** Acute hepatic necrosis with fatty changes is common in patients receiving high doses (>2 g/day) intravenously. It is more likely to occur in pregnant women.
6. **Renal toxicity:** Demeclocycline may produce **nephrogenic** diabetes insipidus by **inhibiting the action of antidiuretic hormone** (ADH) on the collecting duct.
7. **Hypersensitivity reactions.**

Therapeutic uses

1. **In dentistry:** Tetracyclines are used as an adjuvant in chronic periodontitis refractory to other antibiotics.

Doxycycline is useful for the **subgingival plaque** as it:

a. **Gets concentrated in the gingival fluid.**
b. **It inhibits collagenase** enzyme and prevents the destruction of connective tissue in the gum.

Tetracyclines may effectively treat acute necrotizing gingivitis or periodontitis alone or in combination with metronidazole.

2. **Rickettsial infections.**
3. **Mycoplasma pneumoniae infections.**
4. **Chlamydial infections.**
5. **Cholera.**
6. **Brucellosis.**
7. **Plague:** Doxycycline is highly effective.
8. **Anthrax and leptospirosis.**
9. **Acne:** Low doses of tetracyclines are used.
10. **Malaria.**

Advantages of doxycycline

1. It can be **administered orally as well as intravenously**.
2. It is highly potent.
3. It is completely absorbed after oral administration.
4. **Food does not interfere with its absorption**.
5. It has a **longer duration** of action ($t/_2$–24 h).
6. The incidence of diarrhoea is **rare** as it does not affect the intestinal flora.
7. It can be safely given to patients with **renal failure**, as it is excreted primarily in bile.

Chloramphenicol

Chloramphenicol is a broad-spectrum antibiotic. Even though chloramphenicol has a broad spectrum of antibacterial activity, its use is limited to only a few conditions because of its dangerous side effect: **bone marrow suppression. (Incidence** of 1 case in 24,000 to 40,000 courses of therapy)

Mechanism of action: Inhibits protein synthesis.

Chloramphenicol is a **bacteriostatic** agent, but it can be bactericidal at high concentrations **against** H. influenzae, N. meningitidis, and S. pneumoniae.

Adverse effects

1.Hypersensitivity reactions.
2.Bone marrow suppression.
3.Gastrointestinal effects: Prolonged use may cause superinfection due to suppression of gut flora.
4.Gray baby syndrome: In neonates, especially premature babies, chloramphenicol can cause a dose-related gray baby syndrome due to reduced **degradation and detoxification of the drug in the liver because of the deficiency of glucuronyl transferase enzyme**. The manifestations are **nausea, vomiting, abdominal distension, diarrhoea, refusal to suck, cyanosis, irritability, and circulatory collapse.** The skin appears ashen gray, hence the name '**gray baby**' syndrome. **Mortality is high**. Therefore, chloramphenicol should be avoided in neonates.

Therapeutic uses

1.Typhoid fever.
2.Bacterial meningitis.
3.Anaerobic infections: It is often used with metronidazole for treating brain, lung, intra-abdominal or pelvic abscesses.
4.Rickettsial infections.
5.Eye and ear infections.

Macrolides

Roxithromycin, clarithromycin, and azithromycin are semisynthetic macrolides.

Mechanism of action
Erythromycin and other macrolides **inhibit protein synthesis**. They are **bacteriostatic,** but at high concentrations, they can act as **bactericidal agents**.

Drug interactions: Erythromycin and clarithromycin are **Enzyme inhibitors**; hence, they increase the blood levels of drugs such as **theophylline, carbamazepine, valproate, warfarin, digoxin, cyclosporine**, etc., and **potentiate their effects.**

Clarithromycin: is administered orally; achieves high concentration inside the cells. It also treats MAC (Mycobacterium Avium Complex), leprosy, and H. pylori infection.

Azithromycin: It can be administered **orally and intravenously**. Azithromycin is more active against H. influenza than erythromycin and clarithromycin. It has a broad tissue distribution and achieves high intracellular concentration. It is better tolerated and longer acting (**single daily dose**) than erythromycin.

Antibacterial Spectrum and therapeutic uses of Macrolides

1. **In dentistry:** Macrolides are **alternatives to penicillins** to treat orodental infections in patients allergic to **beta-lactam antibiotics**. Aerobic and anaerobic gram-positive bacteria can be used to treat and prevent dental infections, gingivitis, periodontitis, orodental abscess, post-extraction infections, etc. **Azithromycin** is preferred because of a **broader spectrum of activity**, high intracellular concentration, better tolerability, and single daily dosing (azithromycin 500 mg o.d. orally for 3–5 days).

2. As a drug of choice in the following conditions:

A. Mycoplasma-pneumoniae infections & Legionnaires' pneumonia.
B. Chlamydial infections:
C. Diphtheria & Pertussis (whooping cough).

3. As an alternative drug in patients who are allergic to penicillin:

A. Prophylactic uses: Before dental procedures to prevent bacterial endocarditis in patients with valvular lesions.
B. Streptococcal infections: Tonsillitis, pharyngitis, otitis media, cellulitis, etc.

Antitubercular Drugs

Tuberculosis (TB) is a chronic infectious disease caused by M. tuberculosis. Mycobacterial infections require prolonged treatment.

Classification

- **First-line antitubercular drugs (standard drugs):**

Isoniazid (H), Rifampin (R), Pyrazinamide (Z), Ethambutol (E), and Streptomycin (S).

- **Second-line antitubercular drugs (reserve drugs):**

Thiacetazone, Cycloserine, Ethionamide, Kanamycin, Capreomycin, Amikacin, Para-aminosalicylic Acid.

- **Others:**

Ciprofloxacin, Levofloxacin, Moxifloxacin, Ofloxacin, Clarithromycin, Rifabutin, Rifapentine.

First-line Antitubercular Drugs:

Isoniazid (INH): **Mechanism of action:** Isoniazid inhibits the biosynthesis of mycolic acids, essential constituents of the mycobacterial cell wall.

Uses: Isoniazid (INH) is a first-line drug for treating TB. It is also used for the chemoprophylaxis of TB.

Adverse effects and drug interactions

1.Hepatotoxicity.

2.Peripheral neuritis: Pyridoxine 10 mg/day is routinely given along with INH to reduce the risk of peripheral neuritis.

3.Other side effects are fever, skin rashes, arthralgia, anaemia, GI disturbances, psychosis, and rarely convulsions.

NOTE:

Isoniazid **inhibits the metabolism** of phenytoin, carbamazepine, warfarin, etc. → , increasing the plasma levels of these drugs, which may result in toxicity.

Rifampin (Rifampicin)

Mechanism of action: Inhibits RNA synthesis. **It has a bactericidal effect.**

Uses: Tuberculosis, Leprosy, Brucellosis.

Adverse effects and drug interactions

Hepatitis, Flu-like syndrome with fever, GI disturbances, Skin rashes, itching, and flushing.

It **stains** various body fluids such as urine, tears, saliva, sweat, sputum, etc., orange-red, which is harmless.

Rifampin is a potent microsomal **enzyme inducer**, reducing the plasma levels of several drugs, such as oral contraceptives (resulting in contraceptive failure), oral anticoagulants, and oral antidiabetic drugs.

Pyrazinamide

Like INH, pyrazinamide inhibits mycobacterial mycolic acid biosynthesis by a different mechanism. The most significant adverse effect of pyrazinamide is dose-dependent **hepatotoxicity, anorexia, nausea, vomiting, fever, and skin rashes.**

Ethambutol

Ethambutol is well absorbed after oral administration, distributed widely in the body, metabolized in the liver, crosses BBB in meningitis, and excreted in the urine.

Optic neuritis is the main adverse effect seen with ethambutol, characterized by decreased visual acuity and color-vision defects **(red–green)**. It should be **avoided** in children below six because they may be unable to report the disturbances in their vision. It is also difficult to test visual acuity in children.

Treatment of Tuberculosis

Short-course chemotherapy

Several short-course regimens of 6–9 months duration are convenient, **highly effective, and less toxic. All regimens have two phases, an intensive phase of 2–3 months and a continuation phase of 4–6 months.**

An example of a short course of chemotherapy of a 6-month duration is given below.

1.Intensive phase: The patient receives intensive treatment with four tuberculocidal drugs daily or thrice weekly for two months. The main objective of this phase is to render the patient non-contagious.

2.Continuation phase: The patient receives two drugs, usually INH and rifampin, daily or thrice weekly for four months. This phase helps to eliminate the remaining bacilli and prevents relapse.

Antileprotic Drugs

Leprosy is a chronic infectious disease caused by Mycobacterium lepra**e**, an acid-fast bacillus.

Drugs used for the treatment of leprosy

Dapsone, clofazimine, rifampin, ethionamide, ofloxacin, minocycline, and clarithromycin are used in Leprosy.

Dapsone: cheapest and most widely used agent for treating leprosy even today.

Adverse effects

The common adverse effects are dose-related **haemolytic anaemia, particularly in patients with G6PD deficiency**. Other side effects are anorexia, nausea, vomiting, fever, headache, allergic dermatitis, itching, peripheral neuropathy, and hepatitis.


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Fungal Infections

Most fungal infections are opportunistic; hence, they are common in diabetes mellitus, cancer, AIDS, pregnancy, and in patients on immunosuppressive therapy such as a prolonged course of corticosteroids, broad-spectrum antibiotics, anticancer drugs, etc.

Classification

1. **Antifungal Polyene antibiotics:** Amphotericin B, nystatin, hamycin (ha-mycin), and griseofulvin.
2. **Antimetabolites:** Flucytosine (Flu-cytosine).
3. **Azoles:**

a. Imid**azoles**: Ketoconazole, miconazole, clotrimazole.
b. Triaz**oles**: Fluconazole, itraconazole, voriconazole.

4. **Allylamine:** Terbinafine.
5. **Echinocandins (Echino-candins):** Caspofungin acetate, micafungin.

Amphotericin B (AMB): is a broad-spectrum antifungal antibiotic. It is effective against Candida, Aspergillus, Blastomyces, etc.

Adverse effects

AMB is the most toxic of all the antifungal agents.

- The acute reactions are fever, chills, headache, dyspnoea, phlebitis at the injection site, nausea and vomiting, etc.
- Anaemia and electrolyte disturbances are commonly seen.
- Nephrotoxicity.
- Hepatotoxicity.
- Headache and convulsions may occur on intrathecal administration.

Uses

Amphotericin B is highly efficacious but highly toxic too. AMB is useful for various systemic fungal infections like aspergillosis, cryptococcosis, sporotrichosis, candidiasis, cryptococcal meningitis, etc.

Nystatin

Nystatin is poorly absorbed from the skin and mucous membranes. It is highly toxic for systemic use. It is used only topically in Candida infections. It is available as suspension, ointment, cream, powder, and tablet.

Uses

1. In dentistry: Nystatin is used topically for oral candidiasis, angular cheilitis, and antibiotic-associated stomatitis.
2. Other uses include oropharyngeal, corneal, conjunctival, and cutaneous candidiasis.

Adverse effects

They include nausea and a bitter taste.

Griseofulvin

Griseofulvin is used orally for dermatophytic infections. It could be more effective topically.

Uses

Griseofulvin has been used to treat dermatophytic infections like tinea (ringworm) infections (Tinea capitis, Tinea barbae, Tinea corporis, Tinea pedis**)**.

Adverse effects

They are headache, rashes, peripheral neuritis, vertigo, blurred vision, and GI effects such as nausea, vomiting, diarrhoea, heartburn, etc.

Flucytosine

Uses

Flucytosine is used in combination with AMB for cryptococcal meningitis.

Adverse effects

These include bone marrow suppression with anaemia, neutropenia, and thrombocytopenia. The other side effects include nausea, vomiting, diarrhoea, alopecia, skin rashes, itching, and rarely hepatitis.

Miconazole and Clotrimazole

They are used topically for dermatophytes and Candida infections. They are available as cream, gel, lotion, solution, spray, vaginal pessary, etc.

Uses

1. **Candida infections**: Clotrimazole is frequently used for the treatment of oropharyngeal candidiasis.

2. Dermatophytic infections: Clotrimazole and miconazole are useful for Tinea pedis and Tinea cruris.

Adverse effects

These are local irritation, itching, or burning. **Miconazole is safe for use during pregnancy.**

Ketoconazole: Ketoconazole (KTZ) is a prototype drug among azoles.

Adverse effects

Ketoconazole is the most toxic among azoles but less harmful than amphotericin B. Anorexia, nausea, and vomiting are the most common side effects. It reduces adrenal cortical steroids, testosterone, and estrogen synthesis, thus causing gynecomastia, oligospermia, loss of libido, male impotence, menstrual irregularities, and amenorrhoea in females.

Uses

1. **Dermatophytosis:** Ketoconazole is used topically.
2. **Candidiasis:** KTZ is useful for oral, esophageal, and vulvovaginal candidiasis.

Fluconazole: It has a broad spectrum of antifungal activity.

Adverse effects

The common side effects are nausea, vomiting, diarrhoea, and abdominal discomfort. **It is contraindicated during pregnancy** because of the **teratogenic effect**. Fluconazole has an enzyme-inhibiting property.

Uses

Candidiasis: Fluconazole is effective in oral, oropharyngeal, oesophageal, cutaneous, and invasive candidiasis.

Itraconazole has a broad spectrum of activity against many fungi, including Aspergillus.

Adverse effects

These are nausea, vomiting, diarrhoea, headache, hepatotoxicity, and hypokalaemia. Itraconazole inhibits CYP3A4 and can increase serum levels of drugs metabolized by this enzyme.

Uses

Itraconazole is an effective antifungal agent but is rarely used in dental practice. It is effective for oesophageal, oropharyngeal, and vaginal candidiasis but is not superior to fluconazole.

Terbinafine

Terbinafine is a fungicidal agent.

Adverse effects

Terbinafine may cause side effects such as nausea, diarrhoea, dyspepsia, and rarely hepatitis.

Uses

1. Dermatophytosis: Terbinafine is very effective against dermatophytes.

2. Candidiasis: Terbinafine is less effective in Candida infections.

Antiviral agents

1. Drugs used against herpetic infection (anti-herpes agents): Acyclovir, Valacyclovir, Famciclovir, Penciclovir, Ganciclovir.

2. Drugs used against HIV infection (antiretroviral agents): Zidovudine, Lamivudine, Tenofovir, Ritonavir, Lopinavir.

3. Anti-influenza agents: Amantadine, Rimantadine, Oseltamivir, Zanamivir.

4. Other antiviral agents: Interferons and ribavirin.

Acyclovir

- Inhibits viral DNA synthesis and viral replication

- It has a high therapeutic index with low toxicity to host cells.

Uses
Gingivostomatitis, herpes labialis, and ulcers in the mouth.
Other uses are genital herpes, chickenpox, and herpes zoster.

Adverse effects
Acyclovir is usually well tolerated. Nausea, vomiting, diarrhoea, and headache are the other side effects.

Anti-influenza Agents

Amantadine

It is an antiviral drug that has an antiparkinsonian effect as well. It inhibits viral replication. Amantadine is used orally for the prophylaxis and treatment of influenza-A virus infection.

Oseltamivir (Osel-tamivir)

It is used orally to treat and prevent influenza A (bird flu) and B virus infections. Adverse effects are nausea, vomiting, and abdominal discomfort.

Zanamivir

It is similar to oseltamivir. Oral bioavailability is low. It is administered by inhalation. Adverse effects are bronchospasm, headache, and dizziness. It should be avoided in patients with airway disease.

Antiretroviral Agents (HIV infection)

Zidovudine: was the first antiretroviral drug approved for treating HIV infection. It is effective against HIV-1 and HIV-2. Zidovudine is orally effective. It is well absorbed from the GI tract, metabolized in the liver, and excreted in the urine. It crosses the placenta and BBB and is also secreted in milk.

Adverse reactions: Bone marrow suppression, anaemia, and neutropenia are the common side effects. Nausea, vomiting, abdominal discomfort, headache, and insomnia are commonly seen during the initial stages of therapy. Long-term therapy may cause hepatotoxicity, myopathy with fatigue, and lactic acidosis.

Zidovudine is used in combination with other antiretroviral drugs for the treatment of AIDS.

Antimalarial Drugs

Malaria is a protozoal infection caused by the genus Plasmodium and transmitted to man by the infected female Anopheles mosquito. Malaria incidence is increasing due to the resistance of vectors to insecticides and drug-resistant parasites. In India, P. vivax and P. falciparum are common.

Drugs

Chloroquine, Primaquine, Mefloquine, Quinine, quinidine, Pyrimethamine.

Adverse effects and contraindications

Chloroquine in antimalarial doses may cause nausea, vomiting, skin rashes, itching, headache and visual disturbances, hypotension, confusion, cardiac arrhythmias, convulsions, and even cardiac arrest. Long-term therapy requires an ophthalmological examination. **It is safe during pregnancy.**

Uses

Chloroquine is the drug of choice for treating an **acute attack** of malaria; It is a very effective **chemoprophylactic** agent for all types of malaria except that caused by chloroquine-resistant strains of P. falciparum.

Other uses are as follows: Amoebiasis, **L**epra reaction, **R**heumatoid **A**rthritis, and **A**utoimmune disorder: discoid lupus erythematosus.

Nitroimidazoles

Nitroimidazoles are metronidazole, tinidazole, ornidazole, etc.

Mechanism of action: Metronidazole can damage microbial DNA and is highly effective against most anaerobic bacteria and protozoa such as E. histolytica, Giardia lamblia, and Trichomonas vaginalis.

Adverse effects are rarely severe to necessitate the discontinuation of the drug, such as anorexia, nausea, metallic taste, dry mouth, allergic reactions, dizziness, vertigo, and confusion.

Disulfiram-like reactions (nausea, vomiting, abdominal cramps, headache, flushing, etc.) may occur with alcohol.

Uses

- **Metronidazole** is highly effective in most **anaerobic infections.**
- **Vincent's angina** (acute ulcerative gingivitis).
- Metronidazole is used to treat alveolar abscesses, **pericoronitis, and periodontitis**.
- In antibiotic-associated **pseudomembranous colitis.**
- In treating **H-pylori infection**, metronidazole is useful in combination with clarithromycin, amoxicillin, and a proton pump inhibitor.
- Metronidazole is the drug of choice for treating all forms of **amoebiasis**.
- It also can be used in **trichomonas vaginitis, giardiasis**, etc.

Tinidazole

Tinidazole has a longer duration of action and better tolerability than metronidazole.

Uses: Orodental infections & Amoebiasis.

Secnidazole (Sec-nidazole): The spectrum, side effects, and mechanism of action of secnidazole are similar to metronidazole.

Ornidazole and Satranidazole (Satra-nidazole) are nitroimidazoles with a longer duration of action and better tolerability than metronidazole. Satranidazole **does not interact with alcohol** (disulfiram-like reaction).

Anthelmintics or antihelminthics: These are a group of antiparasitic drugs that expel parasitic worms (helminths) and other internal parasites from the body by either stunning or killing them without causing significant damage to the host.

Albendazole: Effective against threadworms, roundworms, whipworms, tapeworms, and hookworms.

Side effects: Stomach pain, nausea, vomiting; dizziness, spinning sensation; headache; or temporary hair loss.

Mebendazole: effective against various nematodes.
Side effects: Stomach/abdominal pain, vomiting, diarrhoea, headache, dizziness, or drowsiness may occur.


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Pharmacology

Dentistry College

Corticosteroids

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Year 3

Assistant lecturer

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Corticosteroids

- **The adrenal gland** has a cortex and medulla.
- **Adrenal cortex** secretes steroidal hormones;
- **Adrenal medulla** secretes adrenaline and noradrenaline.

- **Adrenal cortical** hormones are **more important than medullary hormones**.

- Among cortical hormones, **mineralocorticoids** are more essential than **glucocorticoids**.

- **The renin-angiotensin system controls minimal corticoid (e.g., aldosterone) release**.

- There is a **diurnal variation** in the rate of release of ACTH and cortisol (**circadian rhythm**).

- The plasma cortisol levels are highest in the **early hours of the morning** and the **lowest in the late even**ing.

- The **long-term** use of corticosteroids in **large doses** will **decrease ACTH secretion** and gradually cause **adrenal cortical atrophy**. Hence, **sudden** stoppage of corticosteroids after **prolonged** treatment is dangerous and can precipitate acute **adrenal insufficiency**.

Pharmacological actions

- **Corticosteroids** with predominant **sodium and water-retaining** properties, e.g., aldosterone and desoxycorticosterone, are **mineralocorticoids**.
- Corticosteroids with predominant **liver glycogen deposition** and gluconeogenic effects, e.g., hydrocortisone (cortisol) and cortisone, are **glucocorticoids**.
- The two actions (mineralocorticoid and glucocorticoid) **are not** completely separated in naturally occurring steroids, whereas synthetic preparations are available **with selective action**.

Anti-inflammatory effect

They have **potent anti-inflammatory and immunosuppressant effects**. They prevent or suppress the clinical features of inflammation, such as redness, heat, pain, and swelling.

Immunosuppressant effect

- Glucocorticoids have an **immunosuppressant effect**.
- They inhibit both **B-cell and T-cell lymphocyte** functions, and this results in the impairment of humoral and cell-mediated immunity.
- They also **suppress** all types of hypersensitivity or **allergic reactions.**

Abrupt stoppage of glucocorticoid therapy following prolonged use leads to:

- **Flaring up** of the underlying disease being treated.
- **Withdrawal symptoms** like fever, myalgia, arthralgia, malaise, etc.
- **Acute adrenalin sufficiency** on exposure to stress manifests as anorexia, nausea, vomiting, abdominal pain, hypotension, dehydration, hyponatremia, hyperkalemia, etc.

Adverse reactions

- A single dose of glucocorticoids is **practically harmless**; they are **life-saving drugs** for conditions **like anaphylactic shock, acute adrenal insufficiency, etc.**
- Using glucocorticoids in supraphysiological doses **for more than 2–3 weeks** causes undesirable effects.

Most of the adverse effects are **extensions** of pharmacological actions:

1. **Metabolic effects**: Hyperglycaemia, precipitation of diabetes mellitus (DM), or aggravation of pre-existing diabetes.
2. **Cushing's habitus**: Abnormal fat distribution causes peculiar features with moon face, buffalo hump, and thin limbs.
3. **Gastrointestinal tract**: Peptic ulceration.
4. **Salt and water retention**: Mineralocorticoid effect may cause edema.
5. **Muscle**: Steroid treatment can cause hypokalaemia leading to muscle weakness and fatiguability. Long-term steroid therapy leads to steroid myopathy.
6. **Bone**: Osteoporosis.
7. **Growth retardation** in children is more familiar with dexamethasone and betamethasone.
8. **Eye**: Glaucoma and cataract.
9. **Central nervous system**: Nervousness, insomnia, and mood changes can occur; psychosis may be precipitated.
10. **Long-term therapy with steroids leads to immunosuppression.**

Non-endocrinal uses

- Corticosteroids are one of the most important drugs used clinically in various diseases.
- Because of their **dramatic symptomatic relief**, they **are often misused**.
- Non-endocrinal conditions require supraphysiological doses of steroids, which inevitably carry risk.
- The beneficial effects of glucocorticoids are mainly due to their anti-inflammatory and immunosuppressant effects.

USES

1. **Rheumatoid arthritis.**
2. **Osteoarthritis.**
3. **Allergic diseases.**
4. **Bronchial asthma**: They have **anti-inflammatory and antiallergic.**
5. **Renal disease**: Glucocorticoids are the first-line drugs in **nephrotic syndrome.**
6. **Ocular diseases**: They are frequently used to **suppress inflammation**.
7. **Skin diseases** dramatically relieve itching, pain, and inflammation in allergic and other dermatoses.
8. **Hematological disorders**: Autoimmune haemolytic anaemias usually respond to glucocorticoids.
9. **Cerebral edema.**
10. **Intestinal diseases**: They are used in **ulcerative colitis.**
11. **Organ transplantation.**

Relative contraindications for the use of corticosteroids

1. Hypertension.
2. Diabetes mellitus.
3. Peptic ulcer.
4. Tuberculosis.
5. Herpes simplex keratitis.
6. Osteoporosis.
7. Epilepsy.
8. Psychosis.
9. Congestive cardiac failure.
10. Renal failure.
11. Glaucoma.


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Pharmacology

Anticancer

Dentistry College

TIKRIT UNIVERSITY

(2024-2025)

Year 3

Assistant lecturer

FARAH MOHAMMED NAJEEB

Anticancer Drugs

Cancer is a disease of cells characterized by **P**rogressive, **P**ersistent, **P**erverted (abnormal), **P**urposeless, and uncontrolled **P**roliferation of tissues.

Classification of Anticancer Drugs

1. **Alkylating agents:**

a. **Nitrogen mustards**: Mechlorethamine, Cyclophosphamide, Melphalan, Chlorambucil.
b. **Alkyl sulphonate**: Busulphan.
c. **Nitrosoureas**: Carmustine, Lomustine.
d. **Platinum-containing compounds**: Cisplatin, Carboplatin.
e. **Triazene**: Dacarbazine.

2. **Antimetabolites:**

a. **Folate antagonist**: Methotrexate.
b. **Purine antagonists**: 6-Mercaptopurine (6-MP), 6-thioguanine (6-TG).
c. **Pyrimidine antagonists**: 5-Fluorouracil (5-FU), Cytarabine.

3. Natural products

a. **Vinca alkaloids**: Vinblastine, Vincristine.
b. **Epipodophyllotoxins**: Etoposide, Teniposide.
c. **Taxanes**: Paclitaxel, Docetaxel.
d. **Antibiotics**: Actinomycin D, Bleomycin, Mitomycin C, Doxorubicin, Daunorubicin.
e. **Camptothecins**: Topotecan, Irinotecan.
f. **Enzymes: L-A**sparaginase.

4. Miscellaneous agents: Hydroxyurea, Imatinib.

5. Hormones and antagonists: Glucocorticoids, Estrogens, Antioestrogens, Progestins, Androgens, and Antiandrogens.

Toxicity of Anticancer Drugs (Cytotoxic Drugs)

While destroying cancer cells, anticancer drugs also affect rapidly proliferating normal cells. Bone marrow, skin, hair, gastrointestinal mucosa, reticuloendothelial (RE) system, gonads, fetus, etc., are most severely affected.

General toxicity

a. **Bone marrow suppression**
b. **Immunosuppression**
c. **Oral cavity**: Mucositis, oral ulceration, etc.
d. **GIT:** Nausea and vomiting are due to central action (stimulation of CTZ) and peripheral action in the GI tract.

e. **Skin and hair**: Alopecia (loss of hair) is due to damage to hair follicles.
f. **Gonads:** Cytotoxic drugs also affect gonadal cells and cause oligozoospermia and infertility in males and amenorrhoea and infertility in females.
g. **Fetus:** Administration of cytotoxic drugs during pregnancy usually causes abortion or teratogenic effects.
h. **Carcinogenicity** (secondary malignancy): These drugs may rarely cause secondary cancers in some patients, e.g., the development of leukemia in patients with prolonged use of alkylating agents.
i. **Mutagenicity.**

Alkylating Agents

Alkylating agents are Cell-cycle nonspecific (CCNS) drugs. They also have a radiomimetic effect.

Mechanism of action: Inhibits DNA replication Cell death.

Alkylating agents can also bind to proteins and damage them.

Nitrogen Mustards

Cyclophosphamide is a prodrug and is activated in the liver. The final active metabolites derived from cyclophosphamide are phosphoramide mustard. Phosphoramide mustard produces a cytotoxic effect.

Adverse effects

General toxicity: Severe hemorrhagic cystitis. It is associated with dysuria and haematuria.

Uses

Cyclophosphamide is combined with other anticancer agents in treating **lymphomas, chronic lymphocytic leukemia, breast cancer,** etc.

It also has a powerful immunosuppressant effect; hence, it is useful in **rheumatoid arthritis and nephrotic syndrome** and prevents and treats graft rejection during organ transplantation.

Mechlorethamine
It is one of the drugs useful for treating **Hodgkin's disease**.

Chlorambucil
It was the standard treatment for **chronic lymphocytic leukemia** (CLL).

Melphalan
It is effective in **multiple myeloma** and is used in combination with other agents.

Alkyl Sulphonate.
Busulphan (Busulfan)
It was the preferred drug for **chronic myeloid leukemia** (CML). The common side effects are a pigmentation of the skin, interstitial pulmonary fibrosis, and hyperuricemia.

Nitrosoureas

Carmustine and lomustine are highly lipid-soluble drugs; hence, they reach high concentrations in the **CSF**.

Nitrosoureas are mainly used in **brain tumors.**

Platinum-containing Compounds

Cisplatin

It is a CCNS drug and acts on both dividing and resting cells. Cisplatin is administered intravenously.

Mechanism of action: Inside the cell, DNA damage

Cisplatin is highly effective in treating **testicular, ovarian, endometrial, and bladder cancer.** It is also used in **lung and oesophageal cancer.**

Adverse effects

- Cisplatin is the most emetogenic anticancer drug.
- Vomiting can be controlled by 5-HT3 antagonists such as ondansetron.
- Nephrotoxicity, Ototoxicity, Electrolyte disturbances, and Neuropathy are commonly seen with higher doses.
- Rarely, anaphylactic shock may occur. Cisplatin has mutagenic, teratogenic, and carcinogenic properties.

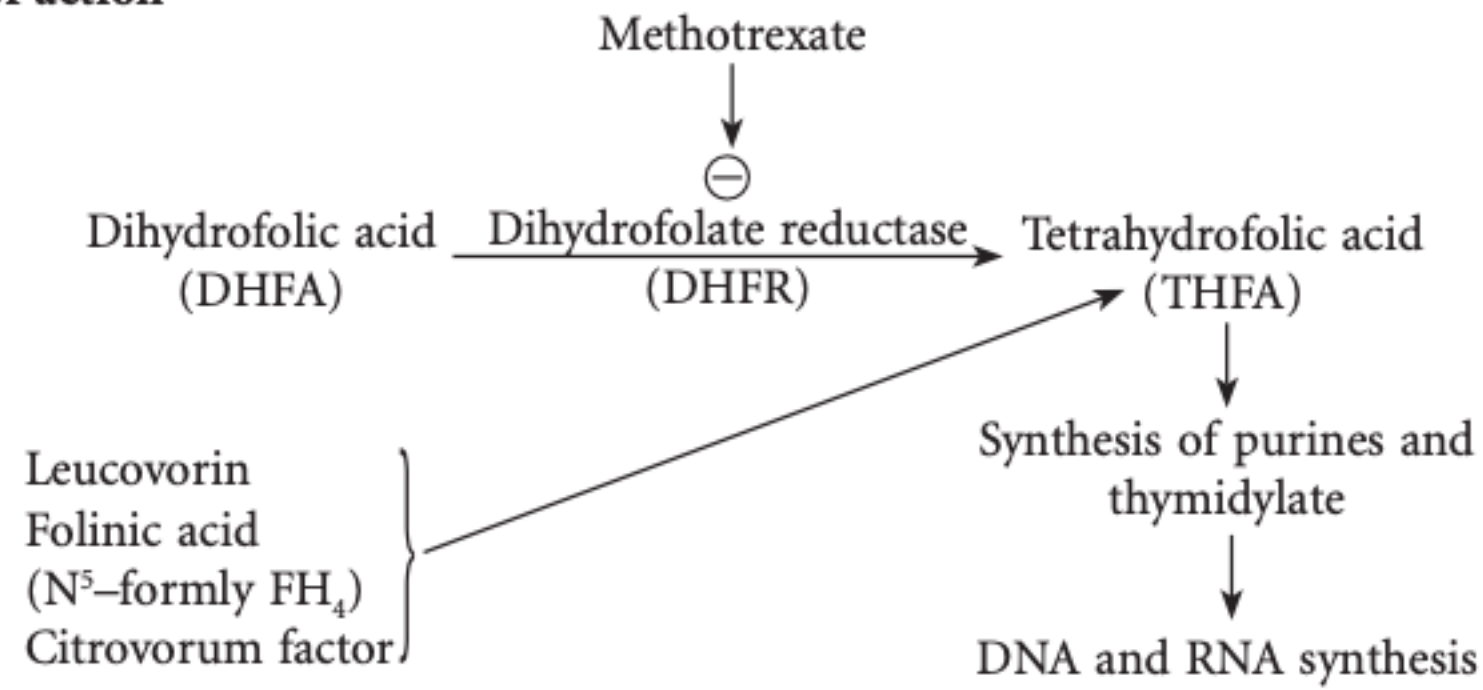
Antimetabolites Folate Antagonist

- **Methotrexate** is one of the most commonly used anticancer drugs.
- It has antineoplastic, immunosuppressant, and anti-inflammatory effects.
- **Methotrexate** is the drug of choice for **choriocarcinoma**.
- It is also used in **acute leukemias**, **Burkitt's lymphoma,** and **breast cancer**.

Adverse effects

Megaloblastic anemia, pancytopenia, hepatic fibrosis, etc.

Mechanism of action



Purine Antagonists: 6-Mercaptopurine (6-MP) and 6-Thioguanine (6-TG)

- 6-MP is used mainly in **acute lymphocytic leukemia**. Bone marrow depression is the major adverse effect of 6-MP.

Pyrimidine Antagonists

- **Fluorouracil (5-FU)** is used in the **gastrointestinal tract (GIT), breast, ovary, skin, recurrent/metastatic salivary gland tumors, etc.**

Anticancer Antibiotics

Anticancer antibiotics have a direct action on DNA and interfere with cell division.

Bleomycin: It is used in **squamous cell carcinoma** of the skin, carcinoma of the oral cavity, and head and neck cancer. Its main side effects are hyperpigmentation of the skin and pulmonary fibrosis.

Doxorubicin and Daunorubicin

Daunorubicin is effective in acute **leukemias**; doxorubicin is active against solid tumors. The side effects are bone marrow suppression, GI disturbances, cardiomyopathy with CCF, hypotension, or arrhythmias.

Actinomycin D

- It is used in the treatment of **Wilm's tumor and choriocarcinoma**.
- Bone marrow suppression and gastrointestinal side effects are prominent.

Mitomycin C

- It mainly treats **GI tumors, cervix, and bladder cancer.**
- It produces bone marrow suppression, gastrointestinal side effects, and nephrotoxicity.

Mithramycin

- It is an anticancer antibiotic that reduces blood calcium levels by inhibiting **osteoclasts**.
- It is used in the treatment of **hypercalcemia with bone metastasis.**

Enzyme
L-Asparaginase

It is used in the treatment of ALL (**acute lymphocytic leukemia**).

Toxicity

1. **H**ypersensitivity reaction with skin rashes, itching, urticaria, etc.
2. **H**yperglycaemia: Due to insulin deficiency.
3. **H**eadache, **H**allucinations, confusion, and coma.
4. **Hemorrhage**: Due to inhibition of synthesis of clotting factors.
5. **Pancreatitis.**

Hormonal Agents

Hormones produce only **palliative effects** in cancer.

1. Glucocorticoids are used in **acute leukemias and lymphomas**.

Apart from this effect, glucocorticoids:

a. Have an anti-inflammatory effect and decreases edema associated with the tumor.
b. Suppress hypersensitivity reaction due to certain anticancer drugs.
c. Control hypercalcaemia.
d. Increase the antiemetic effect of ondansetron & metoclopramide.

2. Others **are estrogens, progestins, tamoxifen, and antiandrogens, finasteride, etc.**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Pharmacology

DENTAL PHARMACOLOGY

Dentistry College

TIKRIT UNIVERSITY

(2024-2025)

Year 3

Assistant lecturer

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DENTAL PHARMACOLOGY

- **Fluoride**

occurs naturally in food and water. It is absorbed mainly in the intestine. It is widely distributed but is concentrated in teeth and bones. The kidney is the major route of excretion. Actions on Teeth Teeth are composed mainly of calcium hydroxyapatite. Fluoride exchanges with hydroxyl ions to form calcium fluorapatite, which is more stable in acid than calcium hydroxyapatite. This makes outer layers of the enamel harder, so the teeth are resistant to acid attack. Fluoride prevents decalcification of enamel by acids and prevents caries. It promotes re-mineralization of enamel, which has been demineralized. It is concentrated in plaque and inhibits microbial enzymes required for acid production.

Use of Fluorides

Dental caries: Caries is a degenerative condition characterized by disintegration of teeth starting from the periphery in the enamel and gradually extending to the pulp/soft tissues. Microorganisms present in the oral cavity act upon residual carbohydrates to produce acids. Acids attack the teeth, leading to demineralization of enamel and, finally, cavitation. There is an increased incidence of dental caries in areas where drinking water is deficient in fluoride. Fluorides are used in the form of fluoridated drinking water, supplements, toothpaste, gel and foam, varnish, and mouthwash.

Fluoridation of Drinking Water

Fluoridated drinking water has an optimal concentration of fluoride and is effective in preventing caries in children and adults. The optimal level of fluoride in drinking water is 1 ppm. This optimal level occurs either naturally or is obtained by the addition of fluoride to community water supply (sodium fluoride is used).

Fluoridated Toothpaste

On brushing, fluoride in toothpaste is taken up by plaque and demineralized enamel. Its concentration is also transiently increased in saliva from where it is taken up by the plaque. Sodium fluoride, sodium monofluorophosphate, and stannous fluoride are the commonly used fluoride salts.

Fluoride Mouth rinse

The fluoride of mouth rinse is retained in the plaque and saliva and helps prevent dental caries. Sodium fluoride 0.20% solution (920 ppm fluoride) and stannous fluoride 0.63% solution is available. They can be used daily or weekly as prescribed by the dentist. Mouth rinse should not be swallowed. To maximise the benefit, patient should be advised not to eat, drink, or rinse the mouth for at least 30 min after using a mouth rinse

Fluoride Supplements

They can reduce the incidence of caries in primary and permanent teeth of children. They are prescribed to children between 6 months and 16 years of age in areas where drinking water is non fluoridated or has low-fluoride content. The decision to prescribe fluoride supplements should be based upon the risk of developing caries, the fluoride content of drinking water, use of other sources of fluoride (toothpaste, mouth rinse), and age of the child. They are not recommended for children below 6 months of age. Irrational use of fluoride supplements can result in fluorosis. Sodium fluoride supplements are available as tablets, lozenges, and liquids. The dose of supplements ranges from 0.25 to 1 mg/day. The tablet/lozenge should be chewed and then swallowed. Dairy products should be avoided 1 h before and after intake of chewable fluoride tablets.

Gel and Foam

Gel of acidulated fluoride phosphate (1.23%), foam or gel (2%) of sodium fluoride, or gel of stannous fluoride is available. A contact time of 4 min is required. They are applied at 3–6-months' interval. Care should be taken not to swallow the preparation.

Fluoride Varnish (5% Sodium Fluoride)

It is applied directly on the teeth by a dentist and is retained on the teeth for hours. A small quantity of the preparation contains a high concentration of fluoride. It is easy to apply; moreover, only small amount of the preparation is required as compared to gel.

Sodium fluoride 5% varnish is commonly used. It is applied at 3–6-month interval, as directed by the dentist.

Fluoride Toxicity

Acute Fluoride Toxicity

It occurs due to accidental ingestion of fluoride-containing insecticides. It manifests as nausea, vomiting, abdominal pain, diarrhoea, hypotension, hypocalcaemia, etc. Gastric lavage is done with calcium salts

to precipitate fluorides. Intravenous glucose is also administered.

Chronic Fluoride Toxicity

Chronic fluoride toxicity, resulting in dental fluorosis, occurs when drinking water has a large amount of fluoride. In mild cases, white opaque spot is seen on the teeth. In severe cases, brown pits are seen on the teeth, giving the teeth an irregular appearance

ASTRINGENTS

Agents that act by reacting with and precipitating proteins in superficial cells to form a protective covering on the surface are called astringents. This covering over the underlying tissue:

(a) protects against bacteria and irritants.

(b) decreases exudation.

(c) arrests capillary oozing when applied to bleeding surfaces.

Types of Astringents

1. Vegetable astringents
2. Metallic astringents
3. Others: Alcohol (not used as astringent in oral cavity)

Vegetable Astringents

Tannic acid: It is a light-brown powder soluble in glycerin and alcohol.

Catechu: Its astringent action is due to the presence of tannic acid.

Metallic Astringents

- Aluminium salts: For example, alum, aluminium acetate. Alum is aluminium potassium sulphate or aluminium ammonium sulphate. It can be used as a solution or powder. As it is acidic, it may damage the enamel. Aluminium acetate is less irritating.
- Zinc salts: For example, zinc chloride, zinc sulphate, zinc oxide. They have astringent and antiseptic properties. They do not stain the teeth. Zinc sulphate is less irritating to the oral mucosa than zinc chloride. The astringent action of zinc oxide is weaker as compared to other zinc salts.
- Ferric chloride: Its use as an astringent has declined as it can stain the teeth and damage the enamel.
- Silver nitrate and copper sulphate: They stain the teeth.

Uses of Astringents

As mouthwash, paint, dentifrices, mummifying agents, obtundents, and styptics in gingivitis, aphthous ulcers, bleeding gums and halitosis.

Dentinal hypersensitivity

is a sharp dental pain usually provoked by thermal, chemical, tactile, or osmotic stimulation of exposed dentinal tubules. These stimuli cause changes in the direction of fluid movement within the dentinal tubules, which is perceived as pain. An ideal desensitising agent should be rapid-acting, have a long duration of action, be non-irritant, be easy to apply, and should not stain the teeth.

Dentinal hypersensitivity is treated by:

1. Desensitising the nerve: By blocking the transmission of neural signals by topical application of potassium nitrate, e.g. 3% potassium nitrate mouth rinse or 5% potassium nitrate tooth paste The exact mechanism of action is not clear. There is an increase in extracellular potassium levels in the dentine cavities, which blocks the generation of action potential in the pulpal nerves.

2. Occluding the dentinal tubules

a. Salts: Stannous fluoride, sodium fluoride, potassium oxalate, strontium chloride, etc. Fluorides, oxalates, and chloride-containing compounds help to seal the surface of the dentine, decrease movement of fluid in the tubules, and diminish dentine hypersensitivity. The application of sodium and stannous fluoride results in the precipitation of calcium fluoride crystals, which act as a barrier in the dentinal tubules. But the calcium fluoride formed dissolves in saliva; hence, it has a transient action. Potassium oxalate reacts with calcium in the dentine to form calcium oxalate on the surface of the dentine and inside the tubules. The drawback of this preparation is that the calcium oxalate formed on the surface is lost following regular brushing of the teeth.

b. Agents that precipitate proteins: Glutaraldehyde, zinc chloride, silver nitrate. By precipitating proteins, they occlude the tubules and decrease movement of fluid. Use of silver nitrate can result in blackening of tooth surface.

c. Resins and dental adhesives seal the open dentine tubules and diminish sensitivity.

Desensitising agents

are available as gel, dentifrices, mouthwash; or they can be applied topically as varnish, adhesives, resin, glass ionomer composite, etc. Depending on the agent, they can be applied either by the patient or the dentist.

Uses: Desensitising agents are used to treat dentinal hypersensitivity due to gingival recession, abrasion and erosion of tooth surface. They can also be used to decrease sensitivity after periodontal treatment. Potassium nitrate can be used before and during tooth bleaching to reduce dentine sensitivity.


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Pharmacology
Anticaries And Drugs Used In Prevention Of Dental Plaque

Dentistry College
TIKRIT UNIVERSITY
(2024-2025)
Year 3
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Dental caries is common in children and young adults but can occur in any age group. There are various ways of controlling dental caries. Primary preventive measures for controlling caries include use of fluorides, pit and fissure sealants, and dietary modification.

Fluorides

Fluorides are effective anticaries agents, and their use has reduced the incidence of dental caries. Fluoride inhibits demineralization and promotes re-mineralization of the enamel. It improves the structure of enamel makes it more acid resistant. It also has antimicrobial actions, thereby inhibiting fermentation of carbohydrates and acid production. Fluorides are administered in the form of fluoridated drinking water, dentifrice, mouth rinse, gel, foam, varnish, and supplements.

Non fluoride Agents

Certain non-fluoride agents may provide some benefit as adjunct to primary prevention measures in children and adults at high risk of developing caries.

Chewing of sucrose-free polyol gum (containing either xylitol only or polyol combinations) for 10–20 min after meals can be used in children (>5 years) and adults at high risk of developing caries.

Xylitol has antimicrobial effects and inhibits acid production in the oral cavity.

A 1:1 mixture of chlorhexidine/thymol varnish may be efficacious in the prevention of root caries in adults and elderly.

Calcium and phosphate in a toothpaste or mouth rinse will increase the concentration of these ions in the oral cavity and improve remineralization. Triclosan has antimicrobial and
Anti inflammatory effects.

Chlorhexidine has broad-spectrum antimicrobial effects. But there is not sufficient evidence that Nonfluoride agents like calcium and/or phosphate agents (with or without casein derivatives), topical chlorhexidine alone, and triclosan can reduce the incidence of caries.

Prevention of Caries

The public, especially children, should be educated about good oral hygiene, proper use of toothbrush, dental floss, etc. Brushing of teeth should be done twice daily. Carbohydrate-containing foods like ice-cream, chocolates, etc. should be avoided. Dental plaque consists of a wide range of bacteria in a matrix of food debris, bacterial polysaccharides and salivary proteins. Plaque plays an important role in the initiation of caries and can cause gingival inflammation, which can progress to periodontal disease. A good antiplaque agent should have prolonged retention time on the oral surface and broad spectrum of antibacterial action with minimal side effects.

The Following Agents Are Used As Mouthwash Or Dentifrice For Their Anti-plaque Actions.

1. Fluorides: Stannous fluoride, sodium fluoride, organic amine fluoride
2. Bis-biguanides: Chlorhexidine, bis-pyridine
3. Quarternary ammonium compounds: Benzalkonium chloride.
4. Phenols and essential oils: Triclosan, thymol, eucalyptol, menthol
5. Enzymes: Amyloglucosidase, glucose oxidase, protease, lipase
6. Antiseptics: Povidone-iodine, chloramine
7. Alkaloids: Sanguarine
8. Detergent: Sodium lauryl sulphate
9. Metals: Zinc, tin
10. Antimicrobials: Penicillin, tetracycline, gramicidin.

Fluorides

Stannous fluoride is more effective than sodium fluoride as an antiplaque agent. Stannous fluoride reduces Streptococcus mutans and Streptococcus sanguis in plaque and S. mutans in saliva. Stannous fluoride-treated enamel is more resistant to colonization by bacteria. It also inhibits bacterial glycolysis by oxidizing thiol group of enzymes involved in the process. It is available as a component of toothpaste and mouthwash.

Adverse effect is staining of the teeth.

Enzymes

Amyloglucosidase and glucoseoxidase activate the lactoperoxidase system in saliva, which converts salivary and exogenous thiocyanate to hypothiocyanite. The formed hypothiocyanite has an inhibitory effect on bacterial growth. Enzymes like dextranases, mutanase, and proteases are plaque-removal agents, but they cause mucosal erosion.

Metal Ions

Zinc ions in the form of citrate and chloride are used as antiplaque agents in toothpaste and mouthwash. Zinc ions inhibit the conversion of glucose to lactic acid by inhibiting the enzymes of glycolysis in bacteria. They also inhibit the enzymes required for glucose uptake by S. sanguis and S. mutans.

Triclosan

It has a broad spectrum of antibacterial effect. It damages the bacterial cytoplasmic membrane, leading to leakage of cellular contents. It also has anti-inflammatory effects. Optimal antiplaque effect is achieved when triclosan is combined with a copolymer. The latter increases the period of retention of triclosan in the oral cavity. Triclosan does not cause staining of the teeth.

Chlorhexidine

It has anti-inflammatory and a broad-spectrum antibacterial effect. It has prolonged oral retention time. Its antiplaque action is decreased by stannous fluoride and sodium lauryl sulphate. Rinsing with chlorhexidine should be avoided after use of toothpaste. Drawbacks are its taste and ability to cause staining of the teeth and tongue.

Essential Oils

Essential oils like thymol, menthol and eucalyptol affect bacterial cell wall to produce antibacterial activity. They help to reduce plaque.

Quarternary Ammonium Compounds

They alter the permeability of the bacterial cell membrane, resulting in leakage of cell contents. They

are effective against both gram-positive and gram-negative bacteria. They are used as mouth rinse. They have a short retention time in the oral cavity.

DENTIFRICES

Agents used with toothbrush to clean and polish the teeth. They can be in the form of paste, gel or powder.

a) An ideal dentifrice:
b) should be non irritant.
c) should not demineralize the enamel.
d) should have pleasant taste and odour.
e) should not produce marked abrasion on the teeth.

The ingredients include:

Active ingredients

1. Anticaries agents
2. Anti calculus agents
3. Antiplaque or anti gingivitis agents
4. Desensitising agents
5. Anti halitosis agents

Inactive ingredients

1. Abrasives
2. Binders
3. Humectants
4. Surfactants/detergents
5. Buffering agents
6. Sweetening agents
7. Flavouring agents
8. Dyes
9. Titanium dioxide
10. Preservatives

Active Ingredients

1. Anticaries agents: They are fluorides like sodium fluoride, sodium monofluorophosphate, amine fluoride and nonfluorides like xylitol, calcium and/or phosphate, metals (zinc, aluminium), etc.

i) Fluorides: Fluoride exchanges with hydroxyl ions to form calcium fluoroapatite, which is more stable in acid than calcium hydroxyapatite. This makes outer layers of the enamel harder, so teeth are resistant to acid attack. It prevents decalcification of enamel by acids and prevents caries. Sodium fluoride and stannous fluoride are the commonly used fluoride salts.

ii) Xylitol: It is a nonfermentable sugar; hence, demineralizing acids are not produced, helping to prevent caries. Xylitol is not used by the bacteria as an energy source, thereby preventing bacterial growth and multiplication. It is present as an anticaries agent in toothpastes and some chewing gums.

2. Anticalculus (antitartar agents): Calculus or tartar is a form of mineralized and hardened dental plaque. It is caused by the continual accumulation of minerals from saliva and gingival fluid on teeth. Anticalculus agents are tetrapotassium and sodium pyrophosphate, zinc compounds, and triclosan/ copolymer.

i) Tetrapotassium and sodium pyrophosphate: They stabilise the calcium level in the saliva and affect the growth of calculus. They also have antimicrobial actions.

ii) Zinc compounds: For example, zinc citrate inhibits plaque formation and bacterial growth. It inhibits crystal growth.

iii) Triclosan/copolymer (poly vinylmethylether/maleic acid): It has antibacterial and anti-inflammatory action, hence reduces plaque formation and gingivitis. The copolymer helps to retain the triclosan intraorally for a longer period of time.

3. Antiplaque (antigingivitis agents): They include triclosan/copolymer, stannous fluoride, zinc citrate, etc.

4. Desensitising agents: They are potassium nitrate, citrate and chloride, stannous fluoride or strontium

chloride. They reduce dentinal hypersensitivity by blocking the transmission of neural signals or occluding dentinal tubules.

5. Antihalitosis agents: They include essential oils, chlorine dioxide, triclosan/copolymer, stannous fluoride, sodium hexametaphosphate. Zinc salts reduce halitosis by inhibiting production of volatile sulphur compounds.

Inactive Ingredients

1. Abrasive agents: For example, calcium carbonate (chalk), dibasic calcium phosphate, silica, magnesium carbonate, aluminium oxide, magnesium trisilicate, etc. They are fi ne powders used to clean and polish the teeth by mechanical action. They should remove debris and stain from the teeth without causing marked abrasion on the teeth.
2. Binding agents: They bind the solid and liquid phases in toothpaste and stabilise the toothpaste. They are not present in toothpowder. They could be natural, e.g. gum arabic, mucilage of tragacanth, bentonite or synthetic like sodium carboxymethyl cellulose, magnesium aluminium silicate, etc.
3. Humectants: They are present in toothpaste only, e.g. glycerine, sorbitol and polypropylene glycol ether. They are also known as antidrying agents. They prevent loss of water from the paste, thus preventing it from becoming hard.
4. Detergents: They generate foam and decrease surface tension. They help to loosen deposits from the surface of teeth while cleaning, breaking down stains and deposits, e.g. sodium lauryl sulphate, sodium lauryl sarcosinate, sodium stearyl fumarate. Sodium lauryl sarcosinate also inhibits hexokinase (an enzyme that converts sugar to acids) and has bacteriostatic action. Sodium lauryl sulphate can cause aphthous ulcers.
5. Buffering agents: They control the pH of the toothpaste, ensuring that it is neither too acidic nor too alkaline. Sodium bicarbonate neutralises acid formed as a result of action of bacteria on food lodged in between the teeth. It also acts as a mild abrasive and helps to remove superficial stains on the teeth. It has antibacterial action.
6. Sweetening agents: They give a sweet taste to the toothpaste and improve its taste, e.g. saccharin sodium, sucrose, lactose, sorbitol, etc. Saccharin is the commonly used sweetener, as it is a non-carbohydrate and does not undergo fermentation. Xylitol is a sweetener that does not undergo fermentation and also has anticaries effect.
7. Flavouring agents: They include peppermint oil, oil of wintergreen in combination with essential oils of clove, eucalyptus, cinnamon, etc. They make the toothpaste more palatable, provide a fresh sensation during and after brushing, and help to mask the taste of detergents.
8. Dyes/Colouring agents: They are used for cosmetic purposes to make the toothpaste attractive, e.g. titanium dioxide for white pastes and food dyes for coloured pastes, e.g. liquor rubri (red colour), methylene blue (blue colour), chlorophyll (green colour), etc.
9. Preservatives: Sodium benzoate, methylparaben and ethylparaben—prevent growth of microorganisms. 10. Whitening agents: Abrasives, enzymes (papain), dimethicone, peroxide, sodium tripolyphosphate are some of the whitening agents present in a toothpaste.

Uses of Dentifrices

To maintain oral hygiene by removal of food debris and plaque—prevent caries, gingivitis, halitosis, periodontal diseases; for removal of stains on the teeth, etc.

BLEACHING AGENTS

Tooth whitening or bleaching has become a popular aesthetic dental treatment. Though both terms are used interchangeably, ‘whitening’ refers to restoration of normal tooth colour whereas ‘bleaching’ results in whitening of the teeth beyond their natural colour. Surface whiteners remove surface stains.

Bleaching

agents are used to remove deep (intrinsic) and surface (extrinsic) stains on the teeth. Tetracycline and high levels of fluorides cause intrinsic staining of the teeth. Extrinsic staining can occur due to aging, smoking, beverages, food, trauma, etc. Demineralization in caries can cause both intrinsic and extrinsic staining of teeth. Bleaching agents can be administered either by the dentist in office or by the patients themselves at home. They are used in the form of trays, strips, toothpaste, mouth rinses, gums, gels, paint-on products, etc. Ideally, tooth bleaching should be done after a proper dental examination and diagnosis, and under professional supervision. The result of bleaching depends on the type of stain, concentration

and contact time of the bleaching agent, frequency of application and age of the patient. The commonly used bleaching agents are primarily peroxides—carbamide peroxide and hydrogen peroxide.

1. **Hydrogen peroxide**: Hydrogen peroxide breaks down into water and free oxygen radicals. The free radicals bind to the stain and decolourise it through an oxidation reaction. The liberation of nascent oxygen is accelerated by application of heat or light. Hydrogen peroxide containing mouthrinse and strips are available.
2. **Carbamide peroxide** (concentration between 10 and 38%): On contact with saliva, it breaks down to liberate hydrogen peroxide (it is the active bleaching agent) and urea. Application of 10% carbamide peroxide in a tray worn for 2 weeks is a commonly used bleaching procedure. A paint-on liquid and gel containing carbamide peroxide is available.
3. **Sodium perborate**: It releases hydrogen peroxide and sodium metaborate. It is combined with hydrogen peroxide (synergistic effect) for internal bleaching (teeth is brightened from the inside— carried out in devitalised teeth).
4. **Calcium peroxide**: It reacts with acid to release hydrogen peroxide. Toothpaste containing calcium peroxide is available.

OBTUNDENTS

Agents that diminish or abolish dentine sensitivity are obtundents. An ideal obtundent should be:

1. Non-irritating to the pulp.
2. Rapid-acting.
3. Easy to apply.
4. Should not stain the teeth.

Mechanism of action: Obtundents act by

a. precipitating proteins within dentinal tubules, e.g. silver nitrate, zinc chloride, ethyl alcohol, paraformaldehyde.

b. paralysing sensory nerve ending, e.g. phenol, camphor, menthol, thymol, etc.

Commonly used obtundents are:

1. Zinc chloride: It is an astringent and acts mainly by precipitating proteins in the dentine. It does not stain the teeth.
2. Silver nitrate: It precipitates proteins but stains the teeth black.
3. Ethyl alcohol (70%): It acts by precipitating proteins. It is nonstaining.
4. Thymol, camphor and menthol: They are volatile oils used in combination and act rapidly. They cause initial stimulation and later paralyse the sensory nerve endings.
5. Clove oil: It initially stimulates and then paralyses the sensory nerve endings. It may stain the teeth. Eugenol is the main constituent of essential oil obtained from cloves.
6. Phenol: It acts by paralysing sensory nerve endings. It acts rapidly and does not stain healthy dentine.
7. Paraformaldehyde: It liberates formaldehyde, which precipitates proteins. It is slow-acting. It may penetrate the pulp and cause infl ammation.

Uses: Obtundents are used to make excavations painless. They are also used to reduce pain in alveolar Osteitis—a gauze containing eugenol (clove oil) along with lignocaine is packed into the affected socket; pain is relieved within minutes.

Disadvantage: Irritant obtundents may shrink the pulp.

MUMMIFYING AGENTS

Agents used to harden and dry the soft tissues of the pulp and root canal. They have antiseptic and astringent properties. Commonly used mummifying agents are:

1. Tannic acid: It is an astringent and precipitates proteins. The tissues are hardened and become
resistant to bacterial infection. It may be used alone or in combination with iodoform or eugenol
and glycerine.
2. Iodoform: It has antiseptic and weak local anaesthetic property. It decomposes to liberate iodine. It is used as a paste in combination with tannic acid, glycerine and eugenol.
3. Liquid formaldehyde: It is an irritant, so it is not used alone. It can cause necrosis of oral tissues.
It is used in combination with zinc oxide, thymol, local anaesthetic and glycerine as a paste.
4. Paraformaldehyde: It acts by liberating formaldehyde. It is used as a paste in combination with zinc oxide, zinc sulphate and glycerine.
5. Cresol: It is used in combination with thymol and zinc oxide as a paste.

Mummifying agents are used when the devitalised pulp and contents of root canal cannot be removed.

MOUTHWASHES (MOUTHRINSES)

A mouthwash is an aqueous solution used to rinse the oral cavity and maintain oral hygiene. Ideal properties of a mouth rinse include low cost, low toxicity, palatability, adequate penetration into plaque, adequate retention at the site of disease, entry into less-accessible areas, stability on storage , and effective antibacterial activity. Cosmetic mouthwash may temporarily suppress bad breath and refresh the mouth with a pleasant taste. Therapeutic mouthwash can help reduce plaque, gingivitis, caries and bad breath.

Mouthwash contains antiseptics (phenolic compounds, bis-guanides, quaternary ammonium compounds, triclosan, halogens, oxygenating agents), astringents, antiplaque, anti tartar, anticaries, desensitising agents, sweeteners, flavouring, colouring agents, detergents, odour neutralisers, etc.

Bisguanide: Chlorhexidine gluconate is a widely used oral product. It is a cationic bisguanide that has **antimicrobial effect**. It decreases pellicle formation and colonisation of enamel by bacteria. It can reduce plaque and gingivitis. It has good substantivity. Adverse effects include unpleasant taste, staining of teeth and restorative materials, calculus deposition, mucosal irritation and taste disturbances. Its efficacy is decreased by sodium lauryl sulphate; hence it should be used 30 min to 2 h after use of toothpaste.

Essential oils: Phenolic compounds containing essential oils like thymol, eucalyptol and menthol kill microorganisms by damaging their cell membrane and inhibiting their enzymes. They scavenge free radicals and also slow down maturation of plaque. They are useful for prevention of plaque, gingivitis and halitosis. Mouthwashes containing essential oils have been used as an adjunct to brushing and flossing to prevent and control plaque formation and gingivitis. Mouthwashes having essential oils contain ethanol. They should not be used in patients with xerostomia or oral mucosal disease because
ethanol can cause mucosal irritation and dryness.

Quaternary ammonium compounds: For example, cetylpyridinium chloride, domiphen bromide. Cetylpyridinium chloride is a cationic agent that binds to and disrupts the bacterial cell membrane. It has been shown to reduce plaque but is less effective and has a lower substantivity than chlorhexidine. Adverse effects include staining of teeth and formation of calculus.

Germicide: Triclosan is a broad-spectrum antibacterial agent that acts by disrupting the microbial cell membrane. It inhibits cyclooxygenase and lipoxygenase to produce an anti-inflammatory effect. It is used in combination with a polymer to improve its antiplaque activity and surface retention.

Oxygenating agents: For example, hydrogen peroxide, sodium perborate. They are broad-spectrum antimicrobials. Hydrogen peroxide is a strong oxidising agent. Preparations containing sodium perborate are available; it reacts with water to produce hydrogen peroxide and borate. They liberate oxygen, which removes light stains and kills anaerobes. They have been shown to reduce gingivitis. They can be used for stain removal and prior to prosthodontic treatment to decrease gingival inflammation.

Povidone-iodine: It is a broad-spectrum antimicrobial agent—active against bacteria, fungi, protozoa and viruses. It can reduce plaque and gingivitis. It is useful as an adjunct with brushing for prevention of plaque formation. It also reduces severity of radiation-induced mucositis.

Fluorides: For example, sodium fluoride, stannous fluoride or acidulated phosphate fluoride. They promote re-mineralization and make the enamel resistant to acid attack. They are prescribed for patients who are at high risk of dental caries. Fluoride mouthwashes are avoided in children less than 6 years of age, as the risk of ingestion is high.

Alcohol: Ethyl alcohol is used in mouthwash as antiseptic, preservative and solvent. Alcohol-free mouthwashes are available. High concentration of alcohol can cause mucosal irritation, ulceration and pain.

- **Detergents**: For example, sodium lauryl sulphate, sodium lauryl sarcosinate. They reduce the surface tension in the oral cavity, thus, allowing other ingredients of mouthwash to come in contact with the teeth easily. They have an anti-plaque effect. By their foaming action, they help to remove food debris from the oral cavity. Sodium lauryl sulphate is a commonly used detergent. Its disadvantage has been the occurrence of aphthous ulcers in some patients. Sodium lauryl sarcosinate is another detergent that is less irritant to the mucosa. Detergent-free mouthwashes are available.
- **Astringents**: For example, zinc chloride, zinc sulphate, tannic acid. They precipitate proteins in the cells to form a protective coat. They are useful in ulcerative gingivitis, aphthous ulcers and chronic alveolar abscess.
- **Antitartar agent**: Zinc compounds prevent buildup of tartar.
- **Flavouring agents**: They are menthol, eucalyptol, peppermint, etc. They improve the flavour of mouthwash, mask the unpleasant taste of ingredients like sodium lauryl sulphate, and provide a sense of freshness inside the mouth.
- **Sweeteners:** Saccharin, sucralose, sorbitol, xylitol are used to impart a mild sweet taste to the mouthwash.
- **Preservatives:** Sodium benzoate and methylparaben are used as preservatives to prevent the growth of microorganisms.
- **Colouring agents** are also used in mouthwashes to improve the appearance. Others:
- **Benzydamine hydrochloride**: It has analgesic, anti-inflammatory, antimicrobial, and anaesthetic properties. It acts by inhibiting prostaglandin synthesis and decreasing cytokine production by macrophages. It has been shown to reduce severity and duration of radiation-induced mucositis for which it is recommended.

Antibacterial peroxidase: Mouthwashes may contain enzymes that act against bacterial peroxidases. The enzymes include glucose oxidase, lactoperoxidase and lysozyme. They can be used for gingivitis and halitosis. These mouthwashes have a low pH, which may result in dental erosion following prolonged use.

Sodium bicarbonate: It is useful in patients with oral ulcers as it does not irritate the oral mucosa. It increases the pH of saliva and suppresses the growth of S. mutans. Anaerobic bacteria produce volatile sulphur compounds, which results in bad breath. Sodium bicarbonate helps to neutralise and mask bad odours

Uses of Mouthwash

- To reduce plaque formation.
- In gingivitis, dental caries and stomatitis.
- To relieve soreness of teeth and gums following fl ossing and use of dentures.
- To reduce bad breath (halitosis).
- To keep the oral cavity moist in xerostomia, as lack of saliva increases the risk of tooth decay.
- To treat oral burns, aphthous ulcers, alveolar osteitis (dry socket) and mucositis following cancer
- chemotherapy and radiotherapy.
- To maintain oral hygiene in persons who are unable to brush adequately owing to their physical disability.

The mouthwash should be swished in the mouth for about 1 min twice/thrice daily and spit out. It should not be swallowed. Patient should be advised not to eat, drink or rinse the mouth for at least 30 min after using a mouthwash

Side Effects

Mouthwash may contain ingredients that cause mucosal irritation and ulcers. They can cause taste disturbances, staining of teeth and restorative materials. Allergies can occur to ingredients of mouthwash. Swallowing fluoride-containing mouthwash can lead to fluoride toxicity. Too much ingestion of alcohol-containing mouthwash can be dangerous in children. There has been concern about the possible risk of oral cancer from long-term use of mouthwash due to alcohol present in it. Excessive use of mouthwash can damage the normal flora in the oral cavity


Thank you
و السلام عليكم و رحمة الله وبركاته

Pharmacology

Dentistry College

DRUG TREATMENT FOR MEDICAL EMERGENCIES

TIKRIT UNIVERSITY

(2024-2025)

Year 3

Assistant lecturer

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DRUG TREATMENT FOR MEDICAL EMERGENCIES

- Dentists must be prepared to manage medical emergencies which may arise in practice. The most important aspect of nearly all medical emergencies in the dental office is to prevent, or correct, insufficient oxygenation of the brain and heart. Therefore, the management of all medical emergencies should include ensuring that oxygenated blood is being delivered to these critical organs.

DRUG	INDICATIONS	PREPARATIONS
Oxygen	For use in all medical emergencies in which hypoxemia may be present	Steel cylinders (green); E tanks, 690 L
Epinephrine	Acute allergic reactions, acute asthma (not responding to adrenergic inhaler)	Ampules, 1 mg; vials, 1 and 30 mg; syringes, 0.3 and 1 mg
Nitroglycerin	Angina pectoris, acute myocardial infarction	Tablets (sublingual), 0.15, 0.3, 0.4, and 0.6 mg; spray, 0.4 mg/actuation
Albuterol	For bronchodilation	Aerosol, 90 µg/ actuation
Glucose	Hypoglycemic episode	Various oral/ transmucosal preparations (orange juice, cake icing, cola)
Aspirin	For reducing platelet aggregation	Chewable aspirin, 81-325 mg

Most common pharmaceutical preparations should be available in each clinic(considered as a life saving medication available in different dosage form and different con)

CATEGORY	REPRESENTATIVE DRUG	PREPARATIONS
Anticonvulsant	Diazepam (Valium)	Ampules and syringes, 10 mg; vials, 10, 20, and 50 mg
Corticosteroid	Hydrocortisone sodium succinate (Solu-Cortef)	Vials, 100, 250, 500 mg, and 1 g
Antihistamine	Diphenhydramine (Benadryl, Benahist, Nordryl)	Ampules, 50 mg; vials, 50, 100, 300, and 500 mg
Respiratory stimulant	Aromatic ammonia spirit (Aromatic Ammonia Aspirols)	Ampules, 0.4 mL

- **Oxygen (O2)** is one of the most important drug in the emergency kit. ideally in an “E”-size cylinder which holds over 600 liters of O2. This size cylinder will not physically be located in the emergency drug kit, but it must be readily available for administration in any emergency situation. It is recommended that, if possible, the emergency drug kit be attached to the O2 cylinder. Indication: Almost any emergency situation. Oxygen may not make the victim better, but it will not make their condition worse

Anaphylactic shock

inj. Adrenaline(1:1000)0.3_0.5 ml i.m.

inj. Hydrocortisone 200 mg i.v

inj. Diphenhydramine 25-50 mg i.v./i.m.

- **Adrenaline (Epinephrine)**

represents the most important drug in the emergency kit. Though (hopefully) rarely used, it must be available for administration as soon as possible in the event of an anaphylactic reaction, and in asthma which does not respond to its drug of first choice, albuterol or salbutamol. Epinephrine (adrenaline) administered rapidly in anaphylaxis has a number of properties that act to save lives in this situation: (1) epinephrine is a potent bronchodilator, reversing bronchospasm (frequently seen in anaphylaxis); (2) it elevates blood pressure and stimulates the myocardium, increasing heart rate, both of which counteract the vasodilation common in anaphylaxis; (3) additionally, in the event of edema formation, epinephrine prevents any further edema from developing that, if intraoral, could lead to airway obstruction or occlusion.

Injectable Histamine-Blocker/Diphenhydramine HCl

A histamine-blocker is also administered in the allergic reaction. Its primary indication is the very common non-life-threatening allergy (itching, hives, rash). A histamine-blocker is also administered in anaphylaxis following epinephrine administration.

Two injectable agents may be considered, either diphenhydramine or chlorpheniramine. They may be administered as part of the management of anaphylaxis or as the sole management of less severe allergic reactions, particularly those with primarily dermatologic signs and symptoms such as urticaria. Recommended doses for adults are 25 to 50 mg of diphenhydramine or 10 to 20 mg of chlorpheniramine.

Corticosteroid

- Administration of a corticosteroid such as hydrocortisone may be indicated for the prevention of recurrent anaphylaxis. Hydrocortisone may also play a role in the management of an adrenal crisis (adrenal insufficiency). The notable drawback in their use in emergencies is their relatively slow onset of action, which approaches one hour even when administered intravenously. This is the reason why these drugs are not considered essential, as they are of minimal benefit in the acute phase of the emergency. There is low likelihood of an adverse response with one dose. The prototype for this group is hydrocortisone, which may be administered in a dose of 200-100 mg as part of the management of these emergencies.

HYPOGLYCEMIA

- **If The Patient Is Conscious Oral Glucose Or Fruit Is Given. If Hypoglycaemia Is Sever (Patient Is Unconscious),50ml Of 50% Dextrose Is Injected Intravenously.**
- **Oral Carbohydrate**

An oral carbohydrate source, such as fruit juice or non-diet soft-drink, should be readily available. Whereas this is not a drug and perhaps should not be included in this list, it should be considered essential. Consideration should be given to making this part of the emergency kit. Its use is indicated in the management of hypoglycaemia in conscious patients.

- **Glucagon**

The presence of this drug allows intramuscular management of hypoglycemia in an unconscious patient. **The ideal management of severe hypoglycaemia in a diabetic emergency is the intravenous administration of 50% dextrose**. Glucagon is indicated if an intravenous line is not in place and venipuncture is not expected to be accomplished, as may often be the case in a dental office. The dose for an adult is 1 mg. If the patient is less than 20 kg, the recommended dose is 0.5 mg. Glucagon is available as a 1 mg formulation, which requires reconstitution with its diluent immediately prior to use.

Adrenal crisis

- Inj. Hydrocortisone 200mg i.v.
- Intravenous normal saline with 5% glucose.
- Correct fluid and electrolyte imbalance.
- An acute adrenal crisis can manifest with vomiting, abdominal pain, and hypovolemic shock. When not promptly recognized, adrenal hemorrhage can be a cause of adrenal crisis. Administration of glucocorticoids in supraphysiologic or stress doses is the only definitive therapy for adrenal crisis.

Acute Attack Of Angina/Myocardial Infarction (Mi)

Tab. Nitroglycerin 0.5 mg sublingually. If the pain is relieved, spit out the tablet. If the pain is not relieved, the tablet can be repeated after 5 min, but not more than three tablets in 15 min. If pain is not relieved, it could be MI. Give the patient a tablet of aspirin 325 mg orally, oxygen by face mask, then refer the patient to a cardiologist.

Nitroglycerin

This drug is indicated for acute angina or myocardial infarction. It is characterized by a rapid onset of action. For emergency purposes, it is available as sublingual tablets or a sublingual spray. One important point to be aware of is that the tablets have a short shelf-life of approximately 3 months once the bottle has been opened and the tablets exposed to air or light. The spray has the advantage of having a shelf-life that corresponds to that listed on the bottle. Therefore, if a patient uses his/her own nitroglycerin, there is a possibility of the drug being inactive. This supports the need for the dentist to always have a fresh supply available. With signs of angina pectoris, one tablet or spray should be administered sublingually. Relief of pain should occur within minutes. If necessary, this dose can be repeated twice more in 5-minute intervals. Systolic blood pressures below 90 mmHg contraindicate the use of this drug.

Aspirin

- Aspirin (acetylsalicylic acid) is one of the more newly recognized life-saving drugs, as it has been shown to reduce overall mortality from acute myocardial infarction.
- The purpose of its administration during an acute myocardial infarction is to prevent the progression from cardiac ischemia to injury to infarction. There is a brief period of time early on during a myocardial infarction where aspirin can show this benefit. For emergency use there are relatively few contraindications. These would include known hypersensitivity to aspirin, severe asthma or history of significant gastric bleeding. The lowest effective dose is not known with certainty, but a minimum of 162 mg should be given immediately to any patient with pain suggestive of acute myocardial infarction.

- **Status asthmaticus (acute severe asthma)**

Humidified oxygen by mask.

Salbutamol 5-10 mg + ipratropium bromide 0.5 mg continuous nebulization.

Inj. Hydrocortisone hemisuccinate 200 mg i.v. and 100 mg 6 hourly till the attack subsides.

Cap. Amoxicillin 500 mg PO TDS.

- **Acute bronchial asthma**

Salbutamol metered dose inhaler (MDI) 100 mcg/puff: 1-2 puffs stat and as and when required (not more than 8 puffs/day).

Albuterol (Salbutamol)

- A selective beta-2 agonist such as albuterol (salbutamol) is the first choice for management of bronchospasm. When administered by means of an inhaler, it provides selective bronchodilation with minimal systemic cardiovascular effects. It has a peak effect in 30 to 60 minutes, with a duration of effect of 4 to 6 hours. Adult dose is 2 sprays, to be repeated as necessary. Pediatric dose is 1 spray, repeated as necessary.

Seizures (epileptic/ drug induced)	Inj. Diazepam 5–10 mg i.v. slowly; repeat the dose, if necessary. Or Inj. Lorazepam 0.1 mg/kg i.v. slowly.

- **Injectable Benzodiazepine**

The management of seizures which are prolonged or recurrent, also known as status epilepticus, may require administration of a benzodiazepine. In most dental practices, it would not be realistic to assume that the dentist could achieve venipuncture in a patient having an active seizure. The benzodiazepines most commonly used to treat status epilepticus are diazepam, lorazepam, and midazolam. Lorazepam has been reported as the drug of choice for status epilepticus and can be administered intramuscularly. Midazolam, however, is another alternative. Sedation would be an expected side effect and patients should be appropriately monitored. Adult doses to consider for lorazepam are 4 mg intramuscularly, or midazolam 5 mg intramuscularly. If an intravenous is in place, these drugs should be slowly titrated to effect.

- **Flumazenil**

The benzodiazepine antagonist flumazenil should be part of the emergency kit when oral or parenteral sedation is used, as these techniques are usually based on effective use of benzodiazepines. Dosage is 0.1 to 0.2 mg intravenously, incrementally.

Tetany	Inject 10–20 mL of 10% calcium gluconate slow intravenously.

- **Tetany** a condition marked by intermittent muscular spasms, caused by malfunction of the parathyroid glands (are four small glands of the endocrine system which regulate the calcium in our bodies) and a consequent deficiency of calcium, or it can be the result of an electrolyte imbalance. Most often, it's a dramatically low calcium level, also known as hypocalcemia.

Fainting	Aromatic ammonia vapouroles held near the nostrils

Hypertensive crisis	Inj. Sodium nitroprusside 0.25–1.5 mcg/kg/min i.v. infusion in 5% dextrose

Thyrotoxic crisis	Tab. Propylthiouracil 150–300 mg PO q6h, Ipodate sodium 0.5 g PO daily, Inj. Propranolol 0.5–2 mg i.v. slowly q4h, Inj. Hydrocortisone 100 mg i.v. q8h.

- **Thyroid storm**, also referred to as thyrotoxic crisis, is an acute, life-threatening, hypermetabolic state induced by excessive release of thyroid hormones (THs) in individuals with thyrotoxicosis. Symptoms include: feeling extremely irritable or grumpy, high systolic blood pressure, low diastolic blood pressure, and fast heartbeat, nausea, vomiting, or diarrhea, high fever, shock and delirium, feeling confused, feeling sleepy, yellow skin or eyes. The primary treatment of thyroid storm is with inorganic iodine and antithyroid drugs (propylthiouracil) to reduce synthesis and release of thyroid hormone. Temperature control and intravenous fluids are also mainstays of management. Beta blockers are often used to reduce the effects of thyroid hormone.

Severe bleeding following dental procedures	• Application of pressure at the site of bleeding • Ice pack • Topical haemocoagulase* solution – applied with a cotton swab. or • Cotton pad soaked in 0.1% adrenaline solution, placed on the bleeding site • Inj. Tranexamic acid 500 mg slow i.v.

*Haemocoagulase enzyme complex is isolated from the venom of *Bothrops atrox* (viper). It promotes coagulation by converting fibrinogen to fibrin. It can also shorten the bleeding and clotting time, thereby reducing blood loss. It is available for topical, intravenous, intramuscular and subcutaneous administration.

Tranexamic acid (is a synthetic reversible competitive inhibitor to the Lysine receptor found on plasminogen. The binding of this receptor prevents plasmin (activated form of plasminogen, it is a non-specific protease usually present in human serum, and it is responsible for degrading a variety of plasma 5

proteins; its specific physiologic role is to degrade fibrin clots) from binding to and ultimately stabilizing the fibrin matrix.

Morphine

Morphine is indicated for the management of **severe pain** which occurs with a myocardial infarction. Advanced Cardiac Life support recommendations list morphine as the analgesic of choice for this purpose. This should be guided by a decrease in blood pressure and respiratory depression. Extreme caution should be used in the elderly. If an intravenous is not in place, consideration can be given to administering morphine in a dose of approximately 5 mg intramuscularly. Again, lower doses need to be considered for the older patient.

Naloxone

If either morphine is included in the emergency kit, or opioids are used as part of a sedation regimen, then naloxene should also be present for the emergency management of inadvertent overdose. Doses should ideally be titrated slowly in 0.1 mg increments to effect.

Nitrous Oxide

Nitrous oxide is a reasonable second choice if morphine is not available to manage pain from a myocardial infarction. For management of pain associated with a myocardial infarction, it should be administered with oxygen, in a concentration approximating 35%, or titrated to effect.


Thank you
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