



Department of Dentistry

Pharmacology

2022-2023

Lecturer

Faris E. Mohammed

Lec. (1)

Pharmacokinetics:

Refers to what the body does to a drug.

Pharmacodynamics:

Describes what the drug does to the body.

Four pharmacokinetic properties determine the onset, intensity, and the duration of drug action.

- **Absorption:**

Absorption from the site of administration permits entry of the drug (either directly or indirectly) into plasma.

- **Distribution:**

The drug may then reversibly leave the bloodstream and distribute into the interstitial and intracellular fluids.

- **Metabolism:**

The drug may be biotransformed by metabolism in the liver or other tissues.

- **Elimination:**

The drug and its metabolites are eliminated from the body in urine, bile, or feces.

Route of administration:

Is determined by the properties of the drug (for example, water or lipid solubility, ionization) and by the therapeutic objectives (for example, the desirability of a rapid onset, the need for long-term treatment, or restriction of delivery to a local site). Major routes of drug administration include enteral, parenteral, and topical.

A. Enteral

Enteral administration (administering a drug by mouth) is the safest and most common, convenient, and economical method of drug administration

B. Parenteral

The parenteral route introduces drugs directly into the systemic circulation. Parenteral administration is used for drugs that are poorly absorbed from the GI tract (for example, heparin) or unstable in the GI tract (for example, insulin).

Intravenous (IV): IV injection is the most common parenteral route. It is useful for drugs that are not absorbed orally, such as the neuromuscular blocker rocuronium.

Intramuscular (IM): Drugs administered IM can be in aqueous solutions, which are absorbed rapidly, or in specialized depot preparations, which are absorbed slowly.

Subcutaneous (SC): Like IM injection, SC injection provides absorption via simple diffusion and is slower than the IV route.

Absorption of Drugs:

Absorption is the transfer of a drug from the site of administration to the bloodstream. The rate and extent of absorption depend on the environment where the drug is absorbed, chemical characteristics of the drug, and the route of administration. Routes of administration other than intravenous may result in partial absorption and lower bioavailability.

Mechanisms of absorption of drugs from the GI tract:

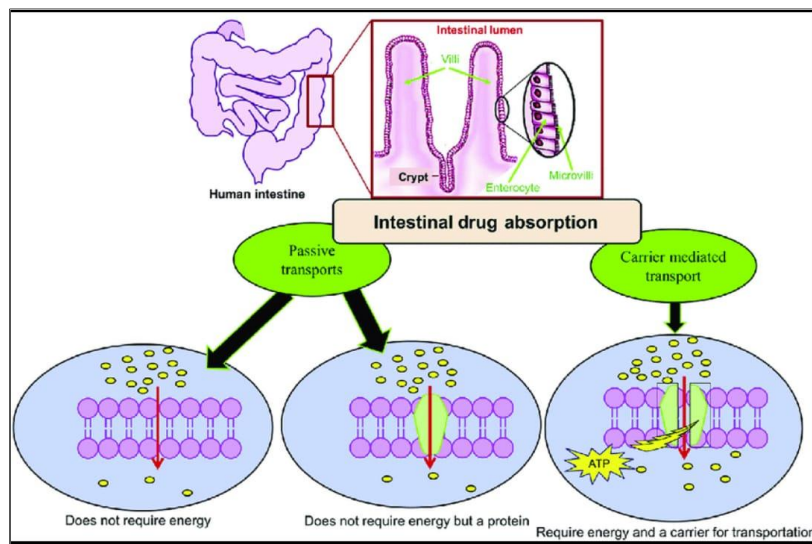
1. Passive diffusion: The driving force for passive absorption of a drug is the concentration gradient across a membrane separating two body compartments. In other words, the drug moves from a region of high concentration to one of lower concentration. The vast majority of drugs are absorbed by this mechanism.

2. Facilitated diffusion: Other agents can enter the cell through specialized transmembrane carrier proteins that facilitate the passage of large molecules. These carrier proteins undergo conformational changes, allowing the passage of

drugs or endogenous molecules into the interior of cells and moving them from an area of high concentration to an area of low concentration.

3. Active transport: This mode of drug entry also involves specific carrier proteins that span the membrane. A few drugs that closely resemble the structure of naturally occurring metabolites are actively transported across cell membranes using specific carrier proteins. It is capable of moving drugs against a concentration gradient, from a region of low drug concentration to one of higher drug concentration.

4. Endocytosis and exocytosis: This type of absorption is used to transport drugs of exceptionally large size across the cell membrane. Endocytosis involves engulfment of a drug by the cell membrane and transport into the cell by pinching off the drug filled vesicle. Exocytosis is the reverse of endocytosis. Many cells use exocytosis to secrete substances out of the cell through a similar process of vesicle formation.



Factors influencing absorption:

1. Effect of pH on drug absorption:

Most drugs are either weak acids or weak bases.

A drug passes through membranes more readily if it is uncharged. Therefore, the effective concentration of the permeable form of each drug at its absorption site is determined by the relative concentrations of the charged and uncharged forms. The ratio between the two forms is, in turn, determined by the pH at the site of absorption and by the strength of the weak acid or base.

2. Contact time at the absorption surface: If a drug moves through the GI tract very quickly, as can happen with severe diarrhea, it is not well absorbed. Conversely, anything that delays the transport of the drug from the stomach to the intestine delays the rate of absorption of the drug. [Note: The presence of food in the stomach both dilutes the drug and slows gastric emptying. Therefore, a drug taken with a meal is generally absorbed more slowly]

3. Expression of P-glycoprotein: P-glycoprotein is a transmembrane transporter protein responsible for transporting various molecules, including drugs, across cell membranes. It is expressed in tissues throughout the body, including the liver, kidneys, placenta, intestines, and brain capillaries, and is involved in transportation of drugs from tissues to blood. That is, it “pumps” drugs out of the cells. Thus, in areas of high expression, P-glycoprotein reduces drug absorption. In addition to transporting many drugs out of cells, it is also associated with multidrug resistance.

Bioavailability:

Is the rate and extent to which an administered drug reaches the systemic circulation. For example, if 100 mg of a drug is administered orally and 70 mg is absorbed unchanged, the bioavailability is 0.7 or 70%. Determining bioavailability is important for calculating drug dosages for non-intravenous routes of administration.

Factors that influence bioavailability:

- **First-pass hepatic metabolism:** When a drug is absorbed from the GI tract, it enters the portal circulation before entering the systemic circulation. If the drug is rapidly metabolized in the liver or gut wall during this initial passage, the amount of unchanged drug entering the systemic circulation is decreased. This is referred to as first-pass metabolism.
- **Solubility of the drug:** Very hydrophilic drugs are poorly absorbed because of their inability to cross lipid-rich cell membranes. Paradoxically, drugs that are extremely lipophilic are also poorly absorbed, because they are totally insoluble in aqueous body fluids and, therefore, cannot gain access to the surface of cells. For a drug to be readily absorbed, it must be largely lipophilic, yet have some solubility in aqueous solutions. This is one reason why many drugs are either weak acids or weak bases.
- **Chemical instability:** Some drugs, such as penicillin G, are unstable in the pH of the gastric contents. Others, such as insulin, are destroyed in the GI tract by degradative enzymes.
- **Nature of the drug formulation:** Drug absorption may be altered by factors unrelated to the chemistry of the drug. For example, particle size, salt form, crystal polymorphism, enteric coatings, and the presence of excipients (such

as binders and dispersing agents) can influence the ease of dissolution and, therefore, alter the rate of absorption.

Drug distribution:

Is the process by which a drug reversibly leaves the blood stream and enters the interstitium (extracellular fluid) and the tissues

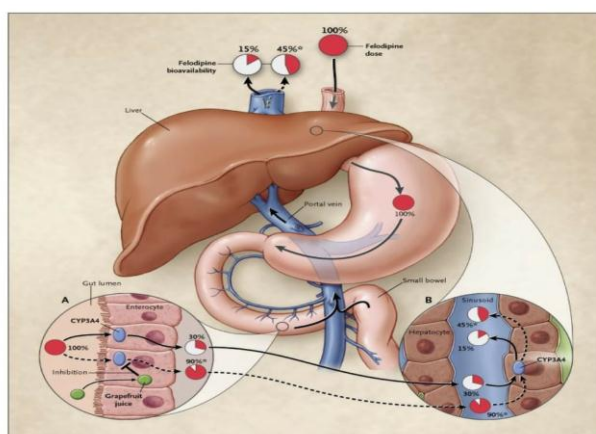
Factors effect drug distribution:

- Blood flow: The rate of blood flow to the tissue capillaries varies widely. For instance, blood flow to the “vessel-rich organs” (brain, liver, and kidney) is greater than that to the skeletal muscles
- Capillary permeability.
- Binding of drugs to plasma proteins and tissues
 1. Binding to plasma proteins:.
 2. Binding to tissue proteins: Many drugs accumulate in tissues, leading to higher concentrations in tissues than in the extracellular fluid and blood
- Lipophilicity The chemical nature of a drug strongly influences its ability to cross cell membranes. Lipophilic drugs readily move across most biologic membranes. These drugs dissolve in the lipid membranes and penetrate the entire cell surface. The major factor influencing the distribution of lipophilic drugs is blood flow to the area. In contrast, hydrophilic drugs do not readily penetrate cell membranes and must pass through slit junctions.
- Volume of distribution:

- **Metabolism:**

Once a drug enters the body, the process of elimination begins. The three major routes of elimination are hepatic metabolism, biliary elimination, and urinary elimination. Together, these elimination processes decrease the plasma concentration exponentially.

Drugs are eliminated according to first-order kinetics, although some, such as aspirin in high doses, are eliminated according to zero-order or nonlinear kinetics. Metabolism leads to production of products with increased polarity, which allows the drug to be eliminated

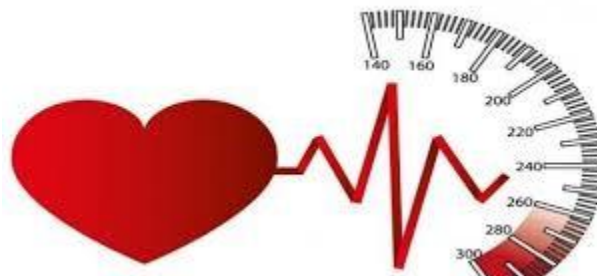
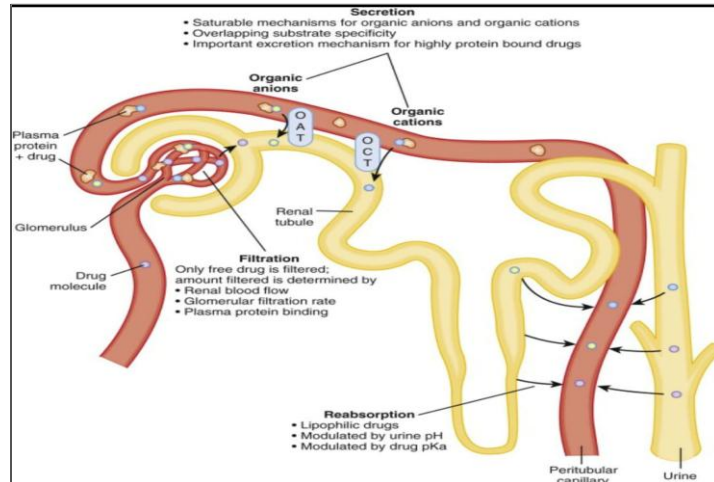


EXCRETION

Drugs must be sufficiently polar to be eliminated from the body. Removal of drugs from the body occurs via a number of routes, the most important being elimination through the kidney into the urine. Patients with renal dysfunction may be unable to excrete drugs and are at risk for drug accumulation and adverse effects

Drug clearance may also occur via the intestines, bile, lungs, and breast milk, among others. Drugs that are not absorbed after oral administration or drugs

that are secreted directly into the intestines or into bile are eliminated in the feces. The lungs are primarily involved in the elimination of anesthetic gases (for example, isoflurane). Elimination of drugs in breast milk may expose the breast-feeding infant to medications and/or metabolites being taken by the mother and is a potential source of undesirable side effects to the infant. Excretion of most drugs into sweat, saliva, tears, hair, and skin occurs only to a small extent. Total body clearance and drug half-life are important measures of drug clearance that are used to optimize drug therapy and minimize toxicity.





Department of Dentistry

Pharmacology

2022-2023

Lecturer

Faris E. Mohammed

Lecture 2

Autonomic nervous system

The nervous system is divided into two anatomical divisions: the central nervous system (CNS), which is composed of the brain and spinal cord, and the peripheral nervous system, which includes neurons located outside the brain and spinal cord. The peripheral nervous system is subdivided into the efferent and afferent divisions. The efferent neurons carry signals away from the brain and spinal cord to the peripheral tissues, and the afferent neurons bring information from the periphery to the CNS.

The efferent portion of the peripheral nervous system is further divided into two major functional subdivisions: the somatic and the ANS.

Autonomic nervous system (ANS):

The ANS, conversely, regulates the everyday requirements of vital bodily functions without the conscious participation of the mind.

The efferent ANS is divided into the **sympathetic** and the **parasympathetic** nervous systems, as well as the enteric nervous system. Anatomically, sympathetic and parasympathetic neurons originate in the CNS and emerge from two different spinal cord regions.

Functions of the sympathetic nervous system:

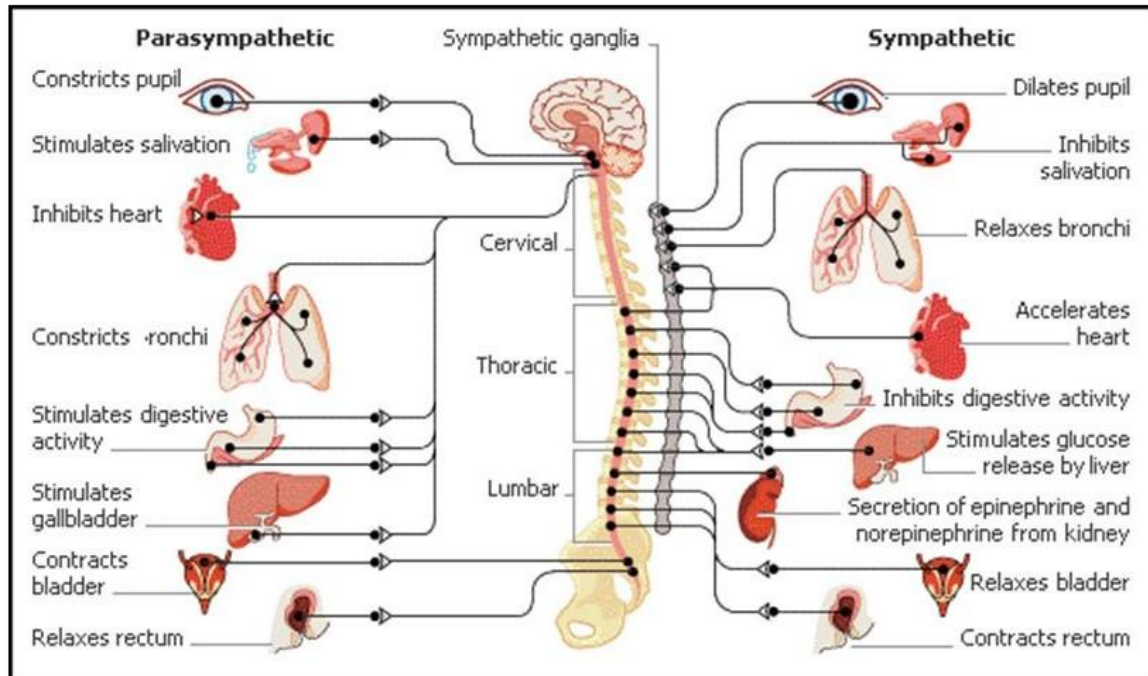
The sympathetic division has the property of adjusting in response to stressful situations, such as trauma, fear, hypoglycemia, cold, and exercise.

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

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 acts to oppose or balance the actions of the sympathetic division and generally predominates the sympathetic system in “rest-and-digest” situations. Unlike the sympathetic system, the parasympathetic system never discharges as a complete system. If it did, it would produce massive, undesirable, and unpleasant symptoms, such as involuntary urination and defecation. Instead parasympathetic fibers innervating specific organs such as the gut, heart, or eye are activated separately, and the system functions to affect these organs individually.

Effects of the Sympathetic and Parasympathetic Divisions of the Autonomic Nervous System



Neurotransmitters:

Communication between nerve cells, and between nerve cells and effector organs, occurs through the release of specific chemical signals (neurotransmitters) from the nerve terminals. This release is triggered by the arrival of the action potential at the nerve ending, leading to depolarization.

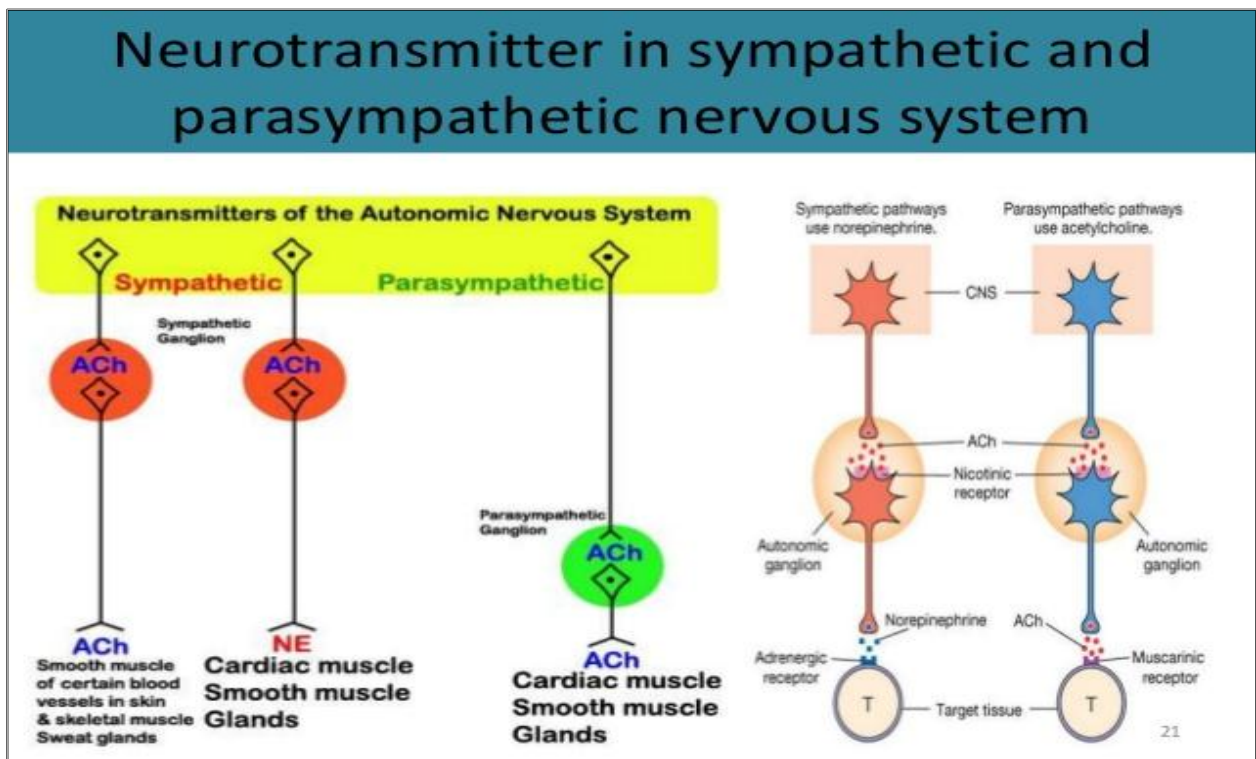
All neurotransmitters are too hydrophilic to penetrate the lipid bilayers of target cell plasma membranes. Instead, their signal is mediated by binding to specific receptors on the cell surface of target organs.

Acetylcholine:

- The autonomic nerve fibers can be divided into two groups based on the type of neurotransmitter released. If transmission is mediated by acetylcholine, the neuron is termed cholinergic.
- Transmission from the autonomic postganglionic nerves to the effector organs in the parasympathetic system,
- Muscarinic Receptors.

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.
- Adrenergic Receptors.



Medication:

A. Direct-acting cholinergic agonists:

Cholinergic agonists mimic the effects of ACh by binding directly to cholinceptors (muscarinic or nicotinic).

These agents may be broadly classified into two groups:

- Endogenous choline esters, which include ACh and synthetic esters of choline, such as carbachol and bethanechol.
- Naturally occurring alkaloids, such as nicotine and pilocarpine.

1. Acetylcholine:

Neurotransmitter of parasympathetic and somatic nerves as well as autonomic ganglia, it lacks therapeutic importance because of its multiplicity of actions (leading to diffuse effects) and its rapid inactivation by the cholinesterases.

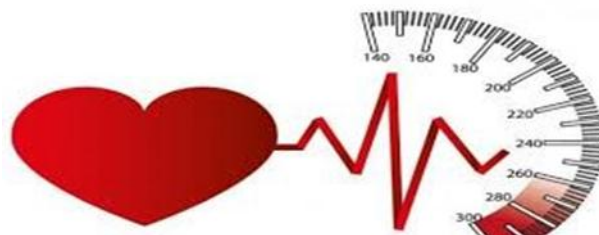
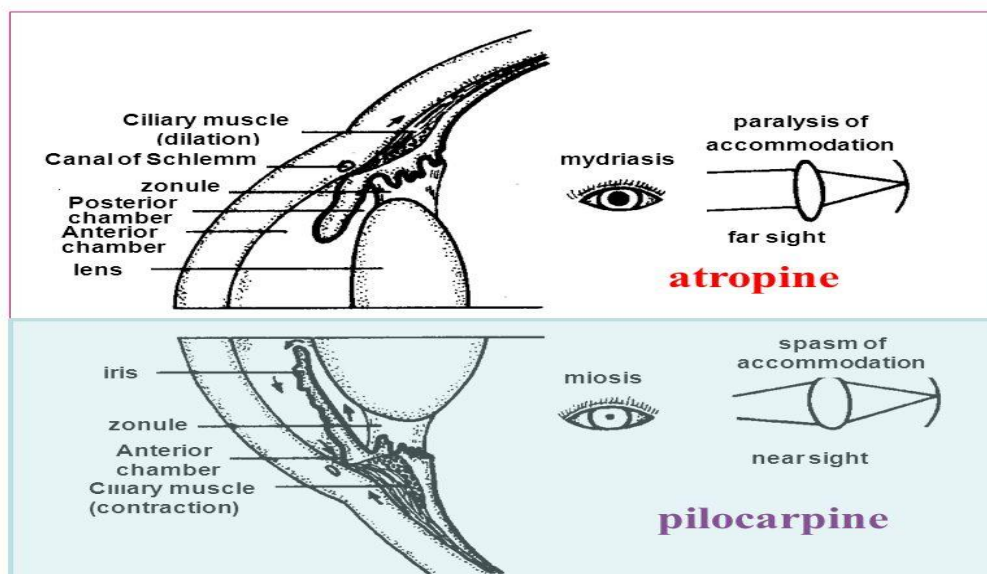
- Decrease in heart rate and cardiac output.
- Decrease in blood pressure.
- Other actions: In the gastrointestinal (GI) tract, acetylcholine increases salivary secretion and stimulates intestinal secretions and motility. It also enhances bronchiolar secretions. In the genitourinary tract, ACh increases the tone of the detrusor muscle, causing urination. In the eye, ACh is involved in stimulation of ciliary muscle contraction for near vision and in the constriction of the pupillae sphincter muscle, causing miosis (marked constriction of the pupil).

2. **Pilocarpine:** Pilocarpine is used to treat glaucoma and is the drug of choice for emergency lowering of intra-ocular pressure of both open-angle and angle-closure glaucoma.

Mechanism of action:

- Miosis
- Pilocarpine is extremely effective in opening the trabecular meshwork around the Schlemm canal, causing an immediate drop in intraocular pressure as a result of the increased drainage of aqueous humor.

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





Department of Dentistry

Pharmacology (Theory)

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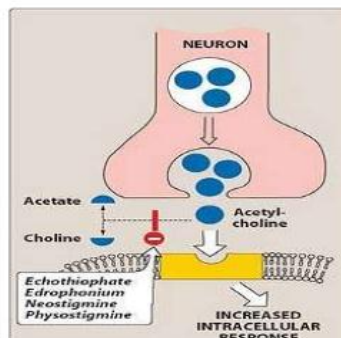
Lecture 3

INDIRECT-ACTING CHOLINERGIC AGONISTS

A. Anticholinesterase Agents (Reversible):

AChE is an enzyme that specifically cleaves ACh to acetate and choline and, thus, terminates its actions. It is located both pre- and postsynaptically in the nerve terminal where it is membrane bound. Inhibitors of AChE (anticholinesterase agents or cholinesterase inhibitors) indirectly provide a cholinergic action by preventing the degradation of ACh. This results in an accumulation of ACh in the synaptic space. Therefore, these drugs can provoke a response at all cholinergic receptors in the body, including both muscarinic and nicotinic receptors of the ANS, as well as at the NMJ and in the brain. The reversible AChE inhibitors can be broadly classified as short-acting or intermediate-acting agents.

Indirect-Acting Cholinergic Agonists Anticholinesterases (Reversible)



Mechanisms of action of indirect (reversible)
cholinergic agonists




1. Physostigmine:

Physostigmine is a nitrogenous carbamic acid ester found naturally in plants and is a tertiary amine. It is a substrate for AChE, and it forms a relatively stable carbamoylated intermediate with the enzyme, which then becomes reversibly inactivated. The result is potentiation of cholinergic activity throughout the body.

Actions: stimulates not only the muscarinic and nicotinic sites of the ANS but also the nicotinic receptors of the NMJ.

Therapeutic uses: The drug increases intestinal and bladder motility, which serves as its therapeutic action in atony of either organ. Physostigmine is also used in the treatment of overdoses of drugs with anticholinergic actions, such as atropine.

Adverse effects:

-  : may lead to convulsions when high doses are used.
-  :Bradycardia and a fall in cardiac output.
-  Inhibition of AChE at the skeletal NMJ causes the accumulation of ACh and ultimately, results in paralysis of skeletal muscle.

2. Neostigmine:

- Synthetic compound that is also a carbamic acid ester and it reversibly inhibits AChE in a manner similar to that of physostigmine.
- Has quaternary nitrogen. Therefore, it is more polar, is absorbed poorly from the GI tract, and does not enter the CNS.

Therapeutic uses:

- It is used to stimulate the bladder and GI tract.
- Antidote for competitive neuromuscular-blocking agents.
- Neostigmine is also used to manage symptoms of myasthenia gravis.

Adverse effects:

Adverse effects include those of generalized cholinergic stimulation, such as salivation, flushing, decreased blood pressure, nausea, abdominal pain, diarrhea, and bronchospasm. Neostigmine does not cause CNS side effects and is not used to overcome toxicity of central-acting antimuscarinic agents such as atropine. Neostigmine is contraindicated when intestinal or urinary bladder obstruction is present.

3. Pyridostigmine:

Cholinesterase inhibitor that is used in the chronic management of myasthenia gravis. Their durations of action are intermediate (3 to 6 hours) but longer than that of neostigmine. Adverse effects of these agents are similar to those of neostigmine.

B. Anticholinesterase Agents (Irreversible):

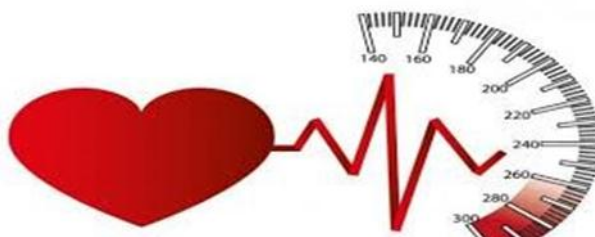
A number of synthetic organophosphate compounds have the capacity to bind covalently to AChE. The result is a long-lasting increase in ACh at all sites where it is released. Many of these drugs are extremely toxic and were developed by the military as nerve agents. Related compounds, such as parathion and malathion, are used as insecticides.

1. Echothiophate:

Mechanism of action: Echothiophate is an organophosphate that covalently binds via its phosphate group at the active site of AChE. Once this occurs, the enzyme is permanently inactivated, and restoration of AChE activity requires the synthesis of new enzyme molecules. Following covalent modification of AChE, the phosphorylated enzyme slowly releases one of its ethyl groups. The loss of an alkyl group, which is called aging, makes it impossible for chemical reactivators, such as pralidoxim.

Therapeutic uses: A topical ophthalmic solution of the drug is available for the treatment of open-angle glaucoma.

2. Organophosphate compounds.





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Pharmacology

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Lecture 4

Anticholinergic





Antimuscarinic Agents:

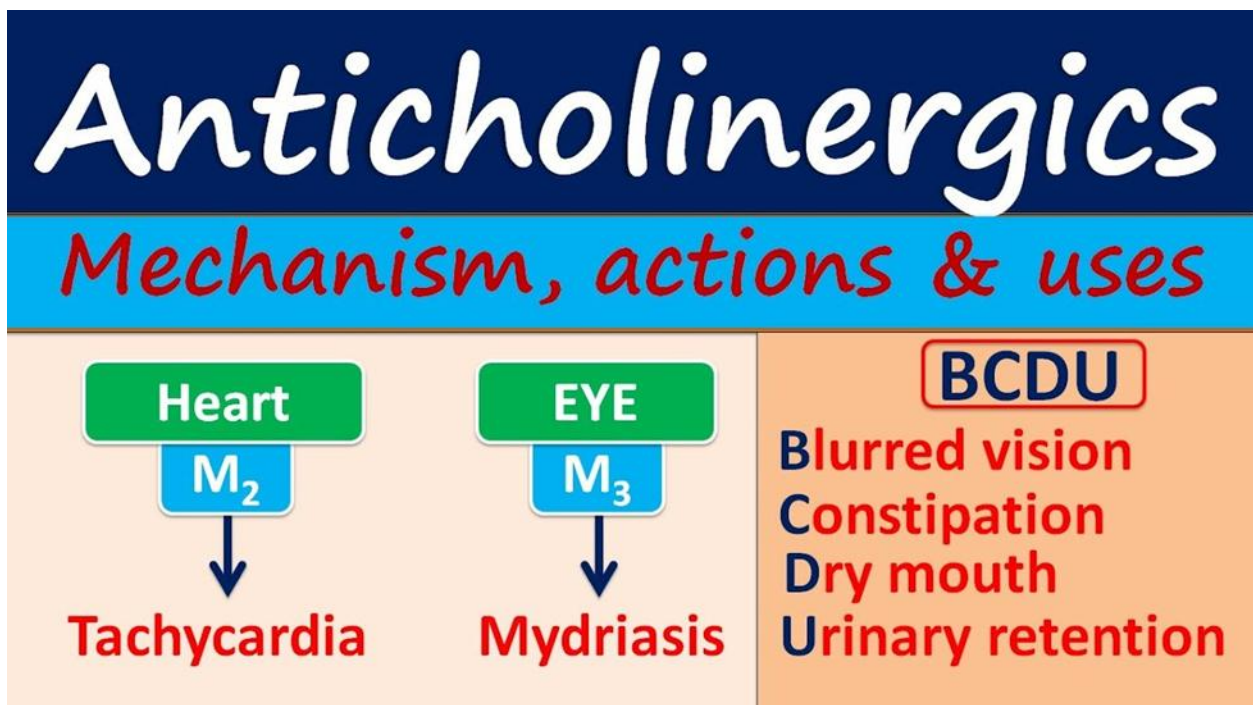
Commonly known as anticholinergic drugs, these agents (for example, atropine and scopolamine) block muscarinic receptors causing inhibition of muscarinic functions.

Atropine:

Atropine is a tertiary amine belladonna alkaloid with a high affinity for muscarinic receptors. It binds competitively and prevents ACh from binding to those sites. Atropine acts both centrally and peripherally. Its general actions last about 4 hours, except when placed topically in the eye, where the action may last for days. The greatest inhibitory effects are on bronchial tissue and the secretion of sweat and saliva.

Action:

-  : Mydriasis (dilation of the pupil), unresponsiveness to light, cycloplegia (inability to focus for near vision).
-  : Antispasmodic to reduce activity of the GI tract.
-  : Higher doses of atropine cause a progressive increase in heart rate by blocking the M2 receptors on the sinoatrial node.
-  : Dryness of the mouth (xerostomia). Sweat and lacrimal glands are similarly affected.



Therapeutic uses:

- **Ophthalmic:** Shorter-acting antimuscarinics (cyclopentolate and tropicamide) have largely replaced atropine due to prolonged mydriasis observed with atropine (7 to 14 days vs. 6 to 24 hours with other agents).
- **Antispasmodic:** Atropine is used as an antispasmodic agent to relax the GI tract.
- **Cardiovascular:** The drug is used to treat bradycardia of varying etiologies.
- **Antisecretory:** Atropine is sometimes used as an antisecretory agent to block secretions in the upper and lower respiratory tracts prior to surgery.
- **Antidote for cholinergic agonists:** organophosphate (insecticides, nerve gases) of overdose of physostigmine, and in some types of mushroom poisoning (certain mushrooms contain cholinergic substances that block cholinesterases). The ability of atropine to enter the central nervous system (CNS) is of particular importance in treating central toxic effects of anticholinesterases.

Adverse effects:

Depending on the dose, atropine may cause dry mouth, blurred vision, “sandy eyes,” tachycardia, urinary retention, and constipation. Effects on the CNS include restlessness, confusion, hallucinations, and delirium, which may progress to depression, collapse of the circulatory and respiratory systems, and death. Low doses of cholinesterase inhibitors, such as physostigmine, may be used to overcome atropine toxicity.

Atropine may also induce troublesome urinary retention. The drug may be dangerous in children, because they are sensitive to its effects, particularly to rapid increases in body temperature that it may elicit.

Hyoscine butylbromide: is an antispasmodic medicine which is taken to relieve cramps in the stomach, intestines or bladder.

Scopolamine:

Scopolamine another tertiary amine plant alkaloid produces peripheral effects similar to those of atropine. However, scopolamine has greater action on the CNS (unlike atropine, CNS effects are observed at therapeutic doses) and a longer duration of action as compared to atropine. It has some special actions as indicated below.

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

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

Ipratropium:

Ipratropium is quaternary derivative of atropine. These agents are approved as bronchodilators for 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 to the pulmonary system.





Department of Dentistry

Pharmacology

2022-2023

Lecturer

Faris E. Mohammed

Lecture 5

Adrenergic

Adrenergic Neuron

Adrenergic neurons release norepinephrine as the primary neurotransmitter, the neurons are found in the central nervous system (CNS) and also in the sympathetic nervous system.

Adrenergic drugs act on adrenergic receptors, located either presynaptically on the neuron or postsynaptically on the effector organ.

Adrenergic receptors (adrenoceptors):

In the sympathetic nervous system, several classes of adrenoceptors can be distinguished pharmacologically. Two main families of receptors, designated α and β are classified on the basis of their responses to the adrenergic agonist's epinephrine, norepinephrine, and isoproterenol. Each of these main receptor types has a number of specific receptor subtypes that have been identified.

α -adrenergic:

- α_1 Receptors (α -adrenergic): postsynaptic involving constriction of smooth muscle.
- α_2 Receptors: presynaptic nerve endings and control the release of norepinephrine.

Stimulation of α_2 receptors causes feedback inhibition and inhibits further release of norepinephrine from the stimulated adrenergic neuron.

β -Adrenoceptors:

- β_1 Heart, causes cardiac stimulation (increase in heart rate and contractility).
- β_2 receptors produces vasodilation (in skeletal muscle vascular beds), smooth muscle relaxation and bronchodilation.

α_1	α_2	β_1	β_2
Vasoconstriction	Inhibition of norepinephrine release	Tachycardia	Bronchodilation
Increased peripheral resistance		Increased lipolysis	Relaxed uterine smooth muscle
Increased blood pressure		Increased myocardial contractility	Increased muscle and liver glycogenolysis
Mydriasis		Increased release of renin	
Increased closure of internal sphincter of the bladder			

DIRECT-ACTING ADRENERGIC AGONISTS

Direct-acting agonists bind to adrenergic receptors on effector organs without interacting with the presynaptic neuron. As a group, these agents are widely used clinically.

Epinephrine:

Epinephrine is one of the four catecholamines (epinephrine, norepinephrine, dopamine, and dobutamine), 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:

- β_1 agonist: cardiac output increases (myocardium contraction).
- α_1 agonist: Epinephrine constricts arterioles in the skin, mucous membranes, and viscera.
- β_2 agonist: Dilates vessels going to the liver and skeletal muscle.

Therapeutic uses:

Bronchospasm:

Epinephrine is the primary drug used in the emergency treatment of respiratory conditions when bronchoconstriction has resulted in diminished respiratory function. Thus, in treatment of acute asthma and anaphylactic shock, epinephrine is the drug of choice and can be lifesaving in this setting. Within a few minutes after subcutaneous administration, respiratory function greatly improves. However, selective β_2 agonists, such as albuterol, are favored in the chronic treatment of asthma because of a longer duration of action and minimal cardiac stimulatory effects.

Anaphylactic shock:

Epinephrine is the drug of choice for the treatment of types I hypersensitivity reactions (including anaphylaxis) in response to allergens.

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

Anesthetics:

Local anesthetic solutions may contain low concentrations (for example, 1:100,000 parts) of epinephrine. Epinephrine greatly increases the duration of local anesthesia by producing vasoconstriction at the site of injection. This allows the local anesthetic to persist at the injection site before being absorbed into the systemic circulation. Very weak solutions of epinephrine can also be applied topically to vasoconstrict mucous membranes and control oozing of capillary blood.

Oxymetazoline:

Oxymetazoline directly stimulates α_1 receptors on blood vessels supplying the nasal mucosa and conjunctiva, thereby producing vasoconstriction and decreasing congestion.

Phenylephrine:

Is a direct-acting, synthetic adrenergic drug that binds primarily to α_1 receptors and acts as a nasal decongestant when applied topically or taken orally.

Salbutamol: Short acting β_2 agonist used primarily as bronchodilators.

Salmeterol and formoterol: Long acting β_2 agonist used as bronchodilators.

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 as its only action. However, the drug can also increase blood pressure significantly by α_1 agonist action on the vasculature, as well as β_1 -stimulatory effects on the heart. Its actions are mediated primarily through an increase in nonvesicular release of catecholamines such as dopamine and norepinephrine from nerve terminals. Thus, amphetamine is an indirect-acting adrenergic drug.

Cocaine:

Cocaine is unique among local anesthetics in having the ability to block the sodium-chloride (Na^+/Cl^-)-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. The duration of action of epinephrine and norepinephrine is increased. Like amphetamines, it can increase blood pressure by α_1 agonist actions and β stimulatory effects.





Pharmacology

Antihypertensive

Lec 6

Lecturer

Faris F. Mohammed

M.Sc. Pharmacology

Cardiovascular System

Antihypertensive

Hypertension is defined as either a sustained systolic blood pressure of greater than 140 mm Hg or a sustained diastolic blood pressure of greater than 90 mm Hg. Hypertension results from increased peripheral vascular arteriolar smooth muscle tone, which leads to increased arteriolar resistance and reduced capacitance of the venous system.

Mechanism of controlling blood pressure

A fall in blood pressure causes pressure-sensitive neurons (baroreceptors in the aortic arch and carotid sinuses) to send fewer impulses to cardiovascular centers in the spinal cord. This prompts a reflex response of increased sympathetic and decreased parasympathetic output to the heart and vasculature, resulting in vasoconstriction and increased cardiac output. These changes result in a compensatory rise in blood pressure.

Mechanism of controlling blood pressure

Baroreceptors in the kidney respond to reduced arterial pressure (and to sympathetic stimulation of β_1 -adrenoceptors) by releasing the enzyme renin. Low sodium intake and greater sodium loss also increase renin release. Renin converts angiotensinogen to angiotensin I, which is converted in turn to angiotensin II, in the presence of angiotensin-converting enzyme (ACE). Angiotensin II is a potent circulating vasoconstrictor, constricting both arterioles and veins, resulting in an increase in blood pressure.

Diuretics

Diuretics can be used as initial drug therapy for hypertension unless there are compelling reasons to choose another agent. Regardless of class, the initial mechanism of action of diuretics is based upon decreasing blood volume, initially by increasing sodium and water excretion. This causes a decrease in extracellular volume, resulting in a decrease in cardiac output and renal blood flow which ultimately leads to decreased blood pressure.

Diuretics

- A. **Thiazide diuretics** (hydrochlorothiazide, chlorthalidone).
- B. **Loop diuretics** (furosemide, torsemide, bumetanide, and ethacrynic acid).

Act promptly by blocking sodium and chloride reabsorption in the kidneys, even in patients with poor renal function or those who have not responded to thiazide diuretics. Loop diuretics cause decreased renal vascular resistance and increased renal blood flow.

Diuretics

C. Potassium-sparing diuretics (spironolactone)

Potassium-sparing diuretics are sometimes used in combination with loop diuretics and thiazides to reduce the amount of potassium loss induced by these diuretics.

2. β -Adrenoceptor–blocking agents

β -Blockers are a treatment option for hypertensive patients with concomitant heart disease or heart failure.

Mechanism of action:

The β -blockers reduce blood pressure primarily by decreasing cardiac output, they may also decrease sympathetic outflow from the central nervous system (CNS) and inhibit the release of renin from the kidneys, thus decreasing the formation of angiotensin II and the secretion of aldosterone.

β -Adrenoceptor–blocking agents

- **Non selective** (propranolol β_1 , β_2)

The nonselective β -blockers, such as propranolol and nadolol, are contraindicated in patients with asthma due to their blockade of β_2 -mediated bronchodilation.

- **Selective** (metoprolol, atenolol β_1)

Adverse effects

1. Common effects: The β -blockers may cause bradycardia, hypotension, and CNS side effects such as fatigue, lethargy, and insomnia. The β -blockers may decrease libido and cause erectile dysfunction, which can severely reduce patient compliance.

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Adverse effect

2. Alterations in serum lipid patterns: Noncardioselective β -blockers may disturb lipid metabolism, decreasing high-density lipoprotein cholesterol and increasing triglycerides.
3. Drug withdrawal: Abrupt withdrawal may induce angina, myocardial infarction, and even sudden death in patients with ischemic heart disease. Therefore, these drugs must be tapered over a few weeks in patients with hypertension and ischemic heart disease.

3. The ACE inhibitors

Angiotensin converting enzyme inhibitors (captopril, enalapril)

Mechanism of action:

1. The ACE inhibitors lower blood pressure by reducing peripheral vascular resistance without reflexively increasing cardiac output, heart rate, or contractility.
2. These drugs block the enzyme ACE which cleaves angiotensin I to form the potent vasoconstrictor angiotensin II.

3. The ACE inhibitors

3. Increase bradykinin levels.

peptide that increases the production of nitric oxide and prostacyclin by the blood vessels. Both nitric oxide and prostacyclin are potent vasodilators.

4. Vasodilation of both arterioles and veins occurs as a result of decreased vasoconstriction (from diminished levels of angiotensin II) and enhanced vasodilation (from increased bradykinin).

3. The ACE inhibitors

Adverse effects:

- a. Rash, fever, altered taste, postural hypotension, hyperkalemia.
- b. Dry cough due to increased levels of bradykinin and substance P in the pulmonary tree and resolves within a few days of discontinuation.

4. Angiotensin II Receptor Blocker

The ARBs, such as losartan and irbesartan, are alternatives to the ACE inhibitors. These drugs block the AT1 receptors, decreasing the activation of AT1 receptors by angiotensin II. Their pharmacologic effects are similar to those of ACE inhibitors in that they produce arteriolar and venous dilation and block aldosterone secretion, thus lowering blood pressure and decreasing salt and water retention, ARBs do not increase bradykinin levels. They may be used as first-line agents for the treatment of hypertension, especially in patients with a compelling indication of diabetes, heart failure, or chronic kidney disease.

Adverse effects

Similar to those of ACE inhibitors, although the risks of cough and angioedema are significantly decreased. ARBs should not be combined with an ACE inhibitor for the treatment of hypertension due to similar mechanisms and adverse effects. These agents are also teratogenic and should not be used by pregnant women.

5. Calcium channel blockers (Verapamil, Diltiazem, nifedipine)

The intracellular concentration of calcium plays an important role in maintaining the tone of smooth muscle and in the contraction of the myocardium. Calcium enters muscle cells through special voltage sensitive calcium channels. This triggers release of calcium from the sarcoplasmic reticulum and mitochondria, which further increases the cytosolic level of calcium.

Mechanism of action

Calcium channel antagonists block the inward movement of calcium by binding to L-type calcium channels in the heart and in smooth muscle of the coronary and peripheral arteriolar vasculature. This causes vascular smooth muscle to relax, dilating mainly arterioles. Calcium channel blockers do not dilate veins.

6. Centrally acting adrenergic drugs

A. Clonidine acts centrally as α_2 agonist to produce inhibition of sympathetic vasomotor centers, decreasing sympathetic outflow to the periphery. This leads to reduced total peripheral resistance and decreased blood pressure.

6. Centrally acting adrenergic drugs

B. Methyldopa is α_2 agonist that is converted to methylnorepinephrine centrally to diminish adrenergic outflow from the CNS. It is mainly used for management of hypertension in pregnancy, where it has a record of safety.





Department of Dentistry

Pharmacology

2022-2023

Lecturer

Faris E. Mohammed

Lecture (7)

Non-narcotic analgesics

Nonsteroidal anti-inflammatory drugs (NSAIDs)

The NSAIDs are a group of chemically dissimilar agents that differ in their antipyretic, analgesic, and anti-inflammatory activities. The class includes derivatives of salicylic acid (aspirin), (ibuprofen fenoprofen, ketoprofen, naproxen, diclofenac, indomethacin, meloxicam.

Aspirin and other NSAIDs

Aspirin can be thought of as a traditional NSAID, but it exhibits anti-inflammatory activity only at relatively high doses that are rarely used. It has gained much more usage at lower doses for the prevention of cardiovascular events such as stroke and myocardial infarction (MI). Aspirin is often differentiated from other NSAIDs, since it is an irreversible inhibitor of cyclooxygenase activity.

Aspirin is a weak organic acid that irreversibly acetylates (and, thus, inactivates) . The other NSAIDs are all reversible inhibitors of cyclooxygenase.

The NSAIDs, including aspirin, have three major therapeutic actions: they reduce inflammation (anti-inflammatory), pain (analgesic effect), and fever.

- A. **Anti-inflammatory actions:** Cyclooxygenase inhibition diminishes the formation of prostaglandins and, thus, modulates aspects of inflammation in which prostaglandins act as mediators. NSAIDs inhibit inflammation in arthritis, but they neither arrest the progression of the disease nor induce remission.
- B. **Analgesic action:** PGE₂ is thought to sensitize nerve endings to the action bradykinin, histamine, and other chemical mediators released locally by the inflammatory process. Thus, by decreasing PGE₂ synthesis, the sensation of pain can be decrease.
The NSAIDs are used mainly for the management of mild to moderate pain arising from musculoskeletal disorders. One exception is ketorolac, which can be used for more severe pain but for only a short duration.
- C. **Antipyretic action:** Fever occurs when the set-point of the anterior hypothalamic thermoregulatory center is elevated. This can be caused by PGE₂ synthesis, which is stimulated when endogenous fever-producing agents (pyrogens), such as cytokines, are released from WBCs that are activated by infection, hypersensitivity, malignancy, or inflammation. The NSAIDs lower body temperature in patients with fever by impeding PGE₂ synthesis and release.

Mechanism of action:

They act primarily by inhibiting the cyclooxygenase enzymes (COX₁) that catalyze the first step in prostanoid biosynthesis. This leads to decreased prostaglandin synthesis with both beneficial and unwanted effects.

COX-1 is a constitutive enzyme that regulates normal cellular processes, such as gastric cytoprotection, vascular homeostasis, platelet aggregation, and reproductive and kidney functions.

COX-2 is constitutively expressed in tissues such as the brain, kidney, and bone. Its expression at other sites. is increased during states of chronic inflammation.

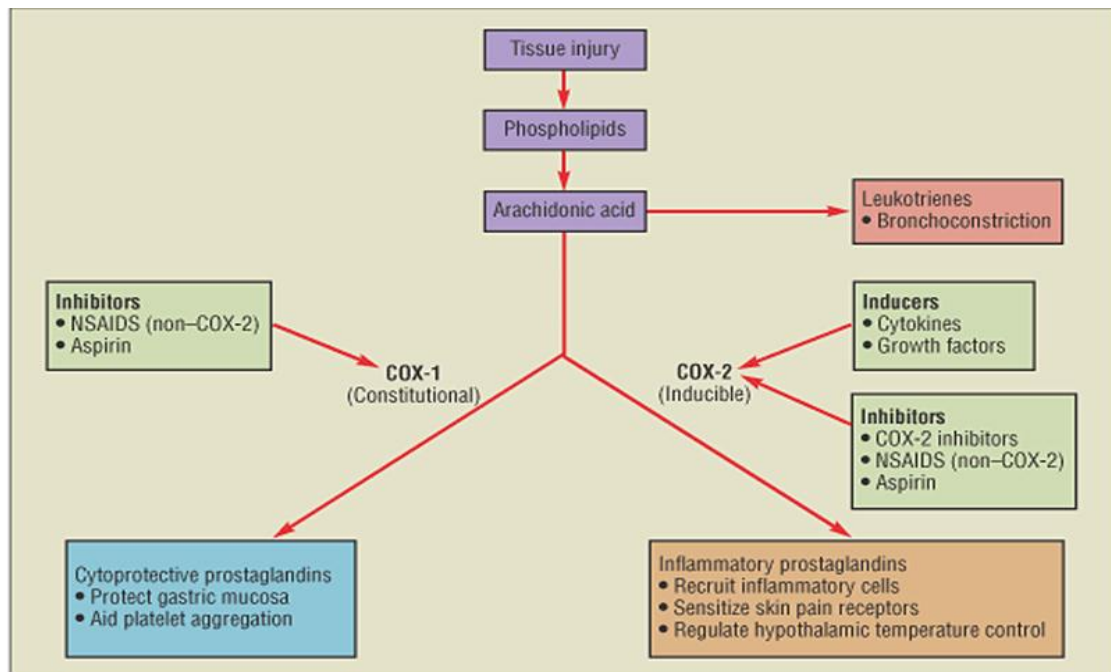


FIGURE 1. Algorithm of the biochemical pathway shows that the formation of prostaglandins occurs via both cyclooxygenase enzymes (COX-1 and COX-2).

1. Aspirin

- High dose: anti-inflammatory, analgesic, anti-pyretic.
- Low dose: anti-platelet prevention of thrombi.

2. Acetaminophen

- Headache: inhibit cyclooxygenase (COX₃) in the brain
- Anti-pyretic.

3. Diclofenac sodium(voltaren), meloxicam, ibuprofen, piroxicam

- Anti inflammatory, analgesic, anti-pyretic
- Diclofenac sodium used for colic pain.

Adverse effects:

A. Gastrointestinal: The most common adverse effects of NSAIDs are GI related, ranging from dyspepsia to bleeding. Normally, production of prostacyclin (PGI₂) inhibits gastric acid secretion, and PGE₂ and PGF₂ α stimulate synthesis of protective mucus in both the stomach and small intestine. Agents that inhibit COX-1 reduce beneficial levels of these prostaglandins, resulting in increased gastric acid secretion, diminished mucus protection, and increased risk for GI bleeding and ulceration. Agents with a higher relative selectivity for COX-1 may have a higher risk for GI events compared to those with a lower relative selectivity for COX-1 (that is, higher COX-2 selectivity). NSAIDs should be taken with food or fluids to diminish GI upset. If NSAIDs are used in patients with a high risk for GI events, proton pump inhibitors or misoprostol should be used concomitantly to prevent NSAID-induced ulcers.

B. Increased risk of bleeding (antiplatelet effect of aspirin).

C. Actions on the kidney: NSAIDs prevent the synthesis of PGE₂ and PGI₂ prostaglandins that are responsible for maintaining renal blood flow. Decreased synthesis prostaglandins can result in retention of sodium and water and may cause edema in some patients. Patients with a history of heart failure or kidney disease are at particularly high risk. These effects can also mitigate the beneficial effects of antihypertensive medications.

D. Risk of elevate blood pressure.

E. Other side effects: NSAIDs are inhibitors of cyclooxygenases and, therefore, inhibit the synthesis of prostaglandins but not of leukotrienes. For this reason, NSAIDs should be used with caution in patients with asthma, as inhibition of prostaglandin synthesis can cause a shift toward leukotriene production and, therefore, increase the risk of exacerbations of asthma.

F. Pregnancy: Most NSAIDs are pregnancy risk category C in the first two trimesters. [Note: Acetaminophen is preferred if analgesic or antipyretic effects are needed during pregnancy.] In the third trimester, NSAIDs should generally be avoided due to the risk of premature closure of the ductus arteriosus.

Contraindicated:

- Asthma: cause bronchospasm because inhibition of benefit prostaglandins.
- Gastro intestinal ulcer because inhibition of benefit prostaglandins.
- Hypertension.

4. Celecoxib

Celecoxib a selective COX-2 inhibitor, is significantly more selective for inhibition of COX-2 than COX-1. Unlike the inhibition of COX-1 by aspirin (which is rapid and irreversible), the inhibition of COX-2 is reversible.

Adverse effects: Headache, dyspepsia, diarrhea, and abdominal pain are the most common.

5. Acetaminophen (N-acetyl-p-aminophenol or APAP)

inhibits prostaglandin synthesis in the CNS. This explains its antipyretic and analgesic properties. Acetaminophen has less effect on cyclooxygenase in peripheral tissues (due to peripheral inactivation), which accounts for its weak anti-inflammatory activity.

Acetaminophen does not affect platelet function or increase bleeding time. It is not considered to be an NSAID.

A. Therapeutic uses Acetaminophen is a suitable substitute for the analgesic and antipyretic effects of NSAIDs for those patients with gastric complaints/ risks, in those whom a prolongation of bleeding time is not desirable, as well as those who do not require the anti-inflammatory action of NSAIDs. Acetaminophen is the analgesic/antipyretic of choice for children with viral infections or chickenpox (due to the risk of Reye syndrome with aspirin).

B. Pharmacokinetics

Acetaminophen is rapidly absorbed from the GI tract. A significant first-pass metabolism occurs in the luminal cells of the intestine and in the hepatocytes. Under normal

circumstances, acetaminophen is conjugated in the liver to form inactive glucuronidated or sulfated metabolites. A portion of acetaminophen is hydroxylated to form N-acetyl-p-benzoquinoneimine, or NAPQI, a highly reactive metabolite that can react with sulfhydryl groups and cause liver damage. At normal doses of acetaminophen, NAPQI reacts with the sulfhydryl group of glutathione, which is produced by the liver, forming a nontoxic substance. Acetaminophen and its metabolites are excreted in urine. The drug is also available in intravenous and rectal formulations.

C. Adverse effects

At normal therapeutic doses, acetaminophen is virtually free of significant adverse effects. With large doses of acetaminophen, the available glutathione in the liver becomes depleted, and NAPQI reacts with the sulfhydryl groups of hepatic proteins, forming covalent bonds. Hepatic necrosis, a very serious and potentially life threatening condition, can result. Patients with hepatic disease, viral hepatitis, or a history of alcoholism are at higher risk of acetaminophen induced hepatotoxicity. [Note: N-acetylcysteine, which contains sulfhydryl groups to which the toxic metabolite can bind, is an antidote in cases of overdose. Acetaminophen should be avoided in patients with severe hepatic impairment.]

Dose of acetaminophen:

Tablet 500 mg (2*4), 4 gm/day maximum daily dose.

150 mg/kg single ingestion (toxic dose).





Department of Dentistry

Pharmacology

2022-2023

Lecturer

Faris E. Mohammed

Lecture (8)

Narcotic analgesics

Opioid analgesics

Opioids are natural, semisynthetic, or synthetic compounds that produce morphine-like effects. All opioids act by binding to specific opioid receptors in the CNS to produce effects that mimic the action of endogenous peptide neurotransmitters (for example, endorphins, enkephalins, and dynorphins).

The major effects of the opioids are mediated by three receptor families, which are commonly designated as μ (mu), κ (kappa), and δ (delta). Each receptor family exhibits a different specificity for the drug(s) it binds. The analgesic properties of the opioids are primarily mediated by the μ receptors that modulate responses to thermal, mechanical, and chemical nociception.

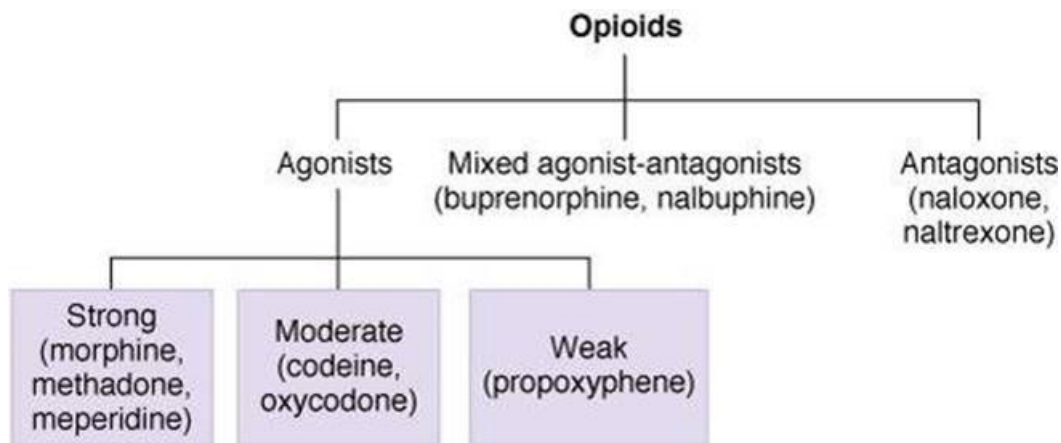
All three opioid receptors are members of the G protein– coupled receptor family and inhibit adenylyl cyclase. They are also associated with ion channels, increasing

postsynaptic K^+ efflux (hyperpolarization) or reducing presynaptic Ca^{2+} influx, thus impeding neuronal firing and transmitter release.

Morphine:

Mechanism of action: Morphine and other opioids exert their major effects by

1. interacting with opioid receptors on the membranes of certain cells in the CNS and other anatomic structures, such as the gastrointestinal (GI) tract and the urinary bladder.
2. It decreases the release of substance P, which modulates pain perception in the spinal cord.
3. Morphine also appears to inhibit the release of many excitatory transmitters from nerve terminals carrying nociceptive (painful) stimuli.



Action:

1. Analgesia: Morphine and other opioids cause analgesia (relief of pain without the loss of consciousness) and relieve pain both by raising the pain threshold at the spinal cord level and, more importantly, by altering the brain's perception of pain. Patients treated with opioids are still aware of the presence of pain, but the sensation is not unpleasant.
2. Euphoria: Morphine produces a powerful sense of contentment and well-being.

3. Respiration: Morphine causes respiratory depression by reduction of the sensitivity of respiratory center neurons to carbon dioxide. This can occur with ordinary doses of morphine in patients who are opioid-naïve and can be accentuated as the dose is increased until ultimately respiration ceases. Respiratory depression is the most common cause of death in acute opioid overdoses. Tolerance to this effect does develop quickly with repeated dosing, which allows the safe use of morphine for the treatment of pain when the dose is correctly titrated.

4. Depression of cough reflex: Both morphine and codeine have antitussive properties. In general, cough suppression does not correlate closely with the analgesic and respiratory depressant properties of opioid drugs. The receptors involved in the antitussive action appear to be different from those involved in analgesia.

5. Miosis: The pinpoint pupil characteristic of morphine use results from stimulation of μ and κ receptors. There is little tolerance to the effect, and all morphine abusers demonstrate pinpoint pupils. [Note: This is important diagnostically, because many other causes of coma and respiratory depression produce dilation of the pupil.]

6. Emesis: Morphine directly stimulates the chemoreceptor trigger zone in the area postrema that causes vomiting.

7. GI tract: Morphine relieves diarrhea by decreasing the motility and increasing the tone of the intestinal circular smooth muscle. Morphine also increases the tone of the anal sphincter. Overall, morphine and other opioids produce constipation, with little tolerance developing. [Note: A nonprescription laxative combination of the stool softener docusate with the stimulant laxative senna is useful to treat opioid-induced constipation.] Morphine can also increase biliary tract pressure due to contraction of the gallbladder and constriction of the biliary sphincter.

8. Cardiovascular: Morphine has no major effects on the blood pressure or heart rate at lower dosages. With large doses, hypotension and bradycardia may occur.

9. Because of respiratory depression and carbon dioxide retention, cerebral vessels dilate and increase cerebrospinal fluid pressure. Therefore, morphine is usually contraindicated in individuals with head trauma or severe brain injury.

10. Histamine release: Morphine releases histamine from mast cells causing urticaria, sweating, and vasodilation. Because it can cause bronchoconstriction, morphine should be used with caution in patients with asthma.

11. Hormonal actions: Morphine increases growth hormone release and enhances prolactin secretion. It increases antidiuretic hormone and leads to urinary retention.

12. Labor: Morphine may prolong the second stage of labor by transiently decreasing the strength, duration, and frequency of uterine contractions.

Adverse effects:

Many adverse effects are common across the entire opioid class. With most μ agonists, severe respiratory depression can occur and may result in death from acute opioid overdose. Elevation of intracranial pressure, particularly in head injury, can be serious. Tolerance and physical dependence. Withdrawal produces a series of autonomic, motor, and psychological responses that incapacitate the individual and cause serious symptoms, although it is rare that the effects cause death.

Fentanyl:

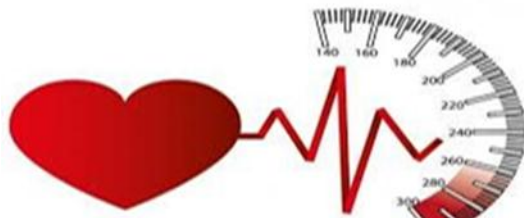
Synthetic opioid has 100-fold the analgesic potency of morphine and is used for anesthesia. The drug is highly lipophilic and has a rapid onset and short duration of action (15 to 30 minutes). It is usually administered IV, epidurally, or intrathecally. Fentanyl is combined

with local anesthetics to provide epidural analgesia for labor and postoperative pain. IV fentanyl is used in anesthesia for its analgesic and sedative effects. An oral transmucosal preparation and a transdermal patch are also available. The oral transmucosal preparation is used in the treatment of cancer patients with breakthrough pain who are tolerant to opioids. Fentanyl is metabolized to inactive metabolites by the CYP450 3A4 system, and drugs that inhibit this isoenzyme can potentiate the effect of fentanyl.

Codeine:

Codeine is a naturally occurring opioid that is a weak analgesic compared to morphine. It should be used only for mild to moderate pain. The analgesic actions of codeine are derived from its conversion to morphine by the CYP450 2D6 enzyme system. Codeine is commonly used in combination with acetaminophen for management of pain. Codeine exhibits good antitussive activity at doses that do not cause analgesia.

Other narcotic analgesic: Methadone, Meperidine.





Department of Dentistry

Pharmacology

2022-2023

Lecturer

Faris E. Mohammed

Lecture 9

General Anesthesia

General anesthesia has three stages: induction, maintenance, and recovery. Induction is the time from administration of a potent anesthetic to development of effective anesthesia. Maintenance provides sustained anesthesia. Recovery is the time from discontinuation of anesthetic until consciousness and protective reflexes return. Induction of anesthesia depends on how fast effective concentrations of anesthetic reach the brain. Recovery is essentially the reverse of induction and depends on how fast the anesthetic diffuses from the brain. Depth of anesthesia is the degree to which the CNS is depressed.

Induction

General anesthesia in adults is normally induced with an IV agent like propofol, producing unconsciousness in 30 to 40 seconds. Additional inhalation and/or IV drugs may be given to produce the desired depth of anesthesia. For children

without IV access, non-pungent agents, such as sevoflurane, are inhaled to induce general anesthesia.

Maintenance

Maintenance of anesthesia after administering the anesthetic, vital signs and response to stimuli are monitored continuously to balance the amount of drug inhaled and/or infused with the depth of anesthesia. Maintenance is commonly provided with volatile anesthetics, which offer good control over the depth of anesthesia. Opioids such as fentanyl are used for analgesia along with inhalation agents, because the latter are not good analgesics. IV infusions of various drugs may be used during the maintenance phase.

Recovery

Postoperatively, the anesthetic admixture is withdrawn, and the patient is monitored for return of consciousness. For most anesthetic agents, recovery is the reverse of induction. Redistribution from the site of action (rather than metabolism of the drug) underlies recovery. The patient is monitored to assure full recovery, with normal physiologic functions (spontaneous respiration, acceptable blood pressure and heart rate, intact reflexes, and no delayed reactions such as respiratory depression).

Mechanism of action

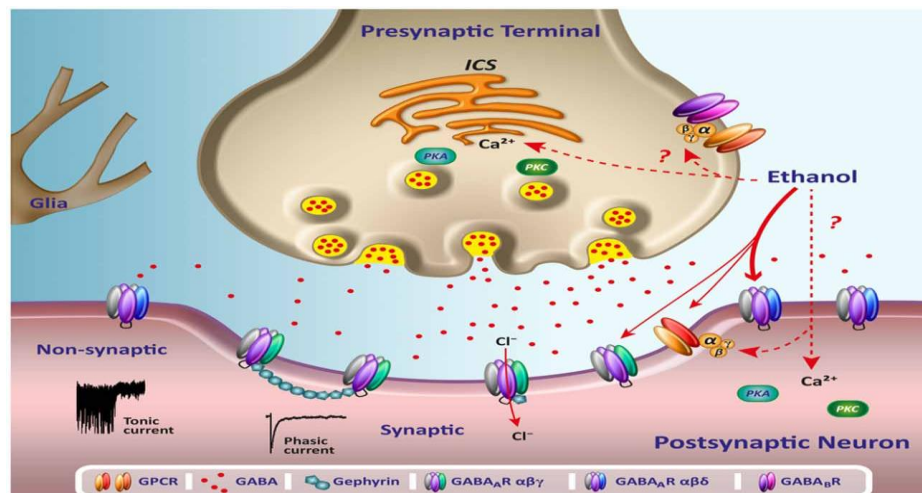
No specific receptor has been identified as the locus of general anesthetic action.

At clinically effective concentrations, general anesthetics

- A. Increase the sensitivity of the γ -aminobutyric acid (GABA_A) receptors to the inhibitory neurotransmitter GABA. This increases chloride ion influx and

hyperpolarization of neurons. Postsynaptic neuronal excitability and, thus, CNS activity are diminished.

- B. Unlike other anesthetics, nitrous oxide and ketamine do not have actions on GABA_A receptors. Their effects are likely mediated via inhibition of the N-methyl-d-aspartate (NMDA) receptors. [Note: The NMDA receptor is a glutamate receptor. Glutamate is the body's main excitatory neurotransmitter.]
- C. Other receptors are also affected by volatile anesthetics. For example, the activity of the inhibitory glycine receptors in the spinal motor neurons is increased.
- D. In addition, inhalation anesthetics block excitatory postsynaptic currents of nicotinic receptors.



Inhalation agent

1. Halothane

Halothane is the prototype to which newer inhalation anesthetics are compared. When halothane was introduced, its rapid induction and quick recovery made it an anesthetic of choice.

Therapeutic uses:

Halothane is a potent anesthetic but a relatively weak analgesic. Thus, it is usually co administered with nitrous oxide, opioids, or local anesthetics. It is a potent bronchodilator. Halothane relaxes both skeletal and uterine muscles and can be used in obstetrics when uterine relaxation is indicated. Halothane is not hepatotoxic in children (unlike its potential effect on adults). Combined with its pleasant odor, it is suitable in pediatrics for inhalation induction, although sevoflurane is now the agent of choice.

Pharmacokinetics:

Halothane is oxidatively metabolized in the body to tissue-toxic hydrocarbons (for example, trifluoroethanol) and bromide ion. These substances may be responsible for toxic reactions that some adults (especially females) develop after halothane anesthesia. This begins as a fever, followed by anorexia, nausea, and vomiting, and possibly signs of hepatitis. Although the incidence is low (approximately 1 in 10,000), half of affected patients may die of hepatic necrosis. To avoid this condition, halothane is not administered at intervals of less than 2 to 3 weeks.

Adverse effects:

1. Cardiac effects:

Atropine-sensitive bradycardia. In addition, halothane has the undesirable property of causing cardiac arrhythmias. Halogenated anesthetics produce concentration-dependent hypotension. This is best treated with a direct-acting vasoconstrictor, such as phenylephrine.

2. Malignant hyperthermia:

In a very small percentage of susceptible patients, exposure to halogenated hydrocarbon anesthetics may induce malignant hyperthermia (MH), a rare life-threatening condition. MH causes a drastic and uncontrolled increase in skeletal muscle oxidative metabolism, overwhelming the body's capacity to supply oxygen, remove carbon dioxide, and regulate temperature, eventually leading to circulatory collapse and death if not treated immediately.

Dantrolene is given as the anesthetic mixture is withdrawn, and measures are taken to rapidly cool the patient. Dantrolene blocks release of Ca^{2+} from the sarcoplasmic reticulum of muscle cells, reducing heat production and relaxing muscle tone.

2. Isoflurane:

This agent undergoes little metabolism and is, therefore, not toxic to the liver or kidney. Isoflurane does not induce cardiac arrhythmias or sensitize the heart to catecholamines. However, like other halogenated gases, it produces dose-dependent hypotension. It has a pungent odor and stimulates respiratory reflexes (for example, breath holding, salivation, coughing, laryngospasm) and is therefore not used for inhalation induction.

3. Desflurane:

Desflurane provides very rapid onset and recovery due to low blood solubility. This makes it a popular anesthetic for outpatient procedures.

4. Sevoflurane:

Sevoflurane has low pungency, allowing rapid induction without irritating the airways. This makes it suitable for inhalation induction in pediatric patients. It has a rapid onset and recovery due to low blood solubility.

5. Nitrous oxide:

Nitrous oxide “laughing gas” is a nonirritating potent analgesic but a weak general anesthetic. It is frequently used at concentrations of 30 to 50% in combination with oxygen for analgesia, particularly in dentistry. Nitrous oxide alone cannot produce surgical anesthesia, but it is commonly combined with other more potent agents. Nitrous oxide is poorly soluble in blood and other tissues, allowing it to move very rapidly in and out of the body. Its speed of movement allows nitrous oxide to retard oxygen uptake during recovery, thereby causing “diffusion hypoxia,” which can be overcome by significant concentrations of inspired oxygen during recovery. Nitrous oxide does not depress respiration and does not produce muscle relaxation. When coadministered with other anesthetics, it has moderate to no effect on the cardiovascular system or on increasing cerebral blood flow, and it is the least hepatotoxic of the inhalation agents. Therefore, it is probably the safest of these anesthetics, provided that sufficient oxygen is administered simultaneously.





Department of Dentistry

Pharmacology

2022-2023

Lecturer

Faris E. Mohammed

Lecture 10

INTRAVENOUS ANESTHETICS

IV anesthetics cause rapid induction often occurring within one “arm– brain circulation time,” or the time it takes to travel from the site of injection (usually the arm) to the brain, where it has its effect. Anesthesia may then be maintained with an inhalation agent. IV anesthetics may be used as sole agents for short procedures or administered as infusions to help maintain anesthesia during longer cases. In lower doses, they may be used for sedation.

a high proportion of initial drug bolus is delivered to the cerebral circulation and then passes along a concentration gradient from blood into the brain. The rate of this transfer is dependent on the arterial concentration of the unbound free drug,

the lipid solubility of the drug, and the degree of ionization. Unbound, lipid-soluble, nonionized molecules cross into the brain most quickly. Once the drug has penetrated the CNS, it exerts its effects.

Propofol:

Propofol is an IV sedative/hypnotic used for induction and/or maintenance of anesthesia. It is widely used and has replaced thiopental as the first choice for induction of general anesthesia and sedation. Because propofol is poorly water soluble, it is supplied as an emulsion containing soybean oil and egg phospholipid, giving it a milk-like appearance.

Onset: Induction is smooth and occurs 30 to 40 seconds after administration. Following an IV bolus, there is rapid equilibration between the plasma and the highly perfused tissue of the brain.

Actions: Although propofol depresses the CNS, it is occasionally accompanied by excitatory phenomena, such as muscle twitching, spontaneous movement, yawning, and hiccups. Transient pain at the injection site is common. Propofol decreases blood pressure without depressing the myocardium. It does not provide analgesia, so supplementation with narcotics is required. The incidence of postoperative nausea and vomiting is very low, as this agent has some antiemetic effects.

Barbiturates:

Thiopental is an ultra-short-acting barbiturate with high lipid solubility. It is a potent anesthetic but a weak analgesic. Thiopental has minor effects on the normal cardiovascular system, but may contribute to severe hypotension in patients with hypovolemia or shock. All barbiturates can cause apnea, coughing, chest wall

spasm, laryngospasm, and bronchospasm (of particular concern for asthmatics). These agents have largely been replaced with newer agents that are better tolerated.

Benzodiazepines:

The benzodiazepines are used in conjunction with anesthetics for sedation. The most commonly used is midazolam.

Diazepam and lorazepam are alternatives. All three facilitate amnesia while causing sedation, enhancing the inhibitory effects of various neurotransmitters, particularly GABA. Minimal cardiovascular depressant effects are seen, but all are potential respiratory depressants (especially when administered IV).

Ketamine:

Ketamine a short-acting anesthetic, induces a dissociated state in which the patient is unconscious (but may appear to be awake) and does not feel pain. This dissociative anesthesia provides sedation, amnesia, and immobility.

Ketamine stimulates central sympathetic outflow, causing stimulation of the heart with increased blood pressure and CO. It is also a potent bronchodilator. Therefore, it is beneficial in patients with hypovolemic or cardiogenic shock and in asthmatics. Conversely, it is contraindicated in hypertensive or stroke patients. The drug is lipophilic and enters the brain very quickly. Like the barbiturates, it redistributes to other organs and tissues. Ketamine is used mainly in children and elderly adults for short procedures. It is not widely used, because it increases cerebral blood flow and may induce hallucinations, particularly in young adults. Ketamine may be used illicitly, since it causes a dream-like state and hallucinations.

Opioids:

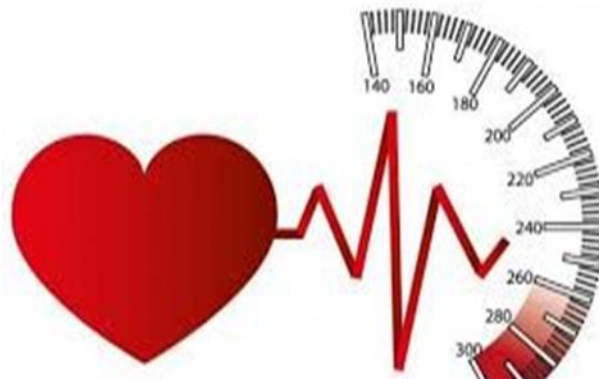
Because of their analgesic property, opioids are commonly combined with other anesthetics. The choice of opioid is based primarily on the duration of action needed. The most commonly used opioids are fentanyl and its congeners, sufentanil and remifentanyl, because they induce analgesia more rapidly than morphine. They may be administered intravenously, epidurally, or intrathecally (into the cerebrospinal fluid). Opioids are not good amnesics, and they can all cause hypotension, respiratory depression, and muscle rigidity, as well as postanesthetic nausea and vomiting. Opioid effects can be antagonized by naloxone.

Etomidate:

Is a hypnotic agent used to induce anesthesia, but it lacks analgesic activity. Induction is rapid, and the drug is short-acting. Among its benefits are little to no effect on the heart and circulation. Etomidate is usually only used for patients with coronary artery disease or cardiovascular dysfunction.

Dexmedetomidine:

is a sedative used in intensive care settings and surgery. It is relatively unique in its ability to provide sedation without respiratory depression.





Department of Dentistry

Pharmacology

2022-2023

Lecturer

Faris E. Mohammed

Lecture 11

LOCAL ANESTHETICS

Local anesthetics block nerve conduction of sensory impulses and, in higher concentrations, motor impulses from the periphery to the CNS.

Na⁺ ion channels are blocked to prevent the transient increase in permeability of the nerve membrane to Na⁺ that is required for an action potential. When propagation of action potentials is prevented, sensation cannot be transmitted from the source of stimulation to the brain.

Delivery techniques:

Include topical administration, infiltration, peripheral nerve blocks, and neuraxial (spinal, epidural) blocks. Small, unmyelinated nerve fibers for pain, temperature, and autonomic activity are most sensitive. Structurally, local anesthetics all include a lipophilic group joined by an amide or ester linkage to a carbon chain, which, in turn, is joined to a hydrophilic group.

The most widely used local anesthetics are **bupivacaine**, **lidocaine**, **mepivacaine**, **procaine**, **ropivacaine**, and **tetracaine**.

Bupivacaine: is noted for cardiotoxicity if inadvertently injected IV. Bupivacaine liposome injectable suspension may provide postsurgical analgesia lasting 24 hours or longer after injection into the surgical site.

Mepivacaine: should not be used in obstetric anesthesia due to its increased toxicity to the neonate.

- A. **Metabolism:** Biotransformation of **amides** occurs primarily in the liver. Prilocaine a dental anesthetic, is also metabolized in the plasma and kidney, and one of its metabolites may lead to methemoglobinemia (defects in the hemoglobin protein itself). **Esters** are biotransformed by plasma cholinesterase (pseudocholinesterase). Patients with pseudocholinesterase deficiency may metabolize ester local anesthetics more slowly. At normal doses, this has little clinical effect. Reduced hepatic function predisposes patients to toxic effects.
- B. **Onset and duration of action:** The onset and duration of action of local anesthetics are influenced by several factors including tissue pH, nerve morphology, concentration, pKa, and lipid solubility of the drug. Of these, the pH of the tissue and pKa are most important. At physiologic pH, these compounds are charged. The ionized form interacts with the protein receptor of the Na⁺ channel to inhibit its function and achieve local anesthesia. The pH may drop in infected sites, causing onset to be delayed or even prevented. Within limits, higher concentration and greater lipid solubility improve onset somewhat. Duration of action depends on the length of time the drug can stay near the nerve to block sodium channels.
- C. **Actions:** Local anesthetics cause vasodilation, leading to rapid diffusion away from the site of action and shorter duration when these drugs are administered alone. By adding the vasoconstrictor epinephrine, the rate of local anesthetic absorption and diffusion is decreased. This minimizes systemic toxicity and increases the duration of action. Hepatic function does not affect the duration of action of local anesthesia, which is determined by redistribution and not biotransformation. Some local anesthetics have other therapeutic uses (for example, lidocaine is an IV antiarrhythmic).
- D. **Allergic reactions:** Patient reports of allergic reactions to local anesthetics are fairly common, but often times reported “allergies” are actually side effects from epinephrine added to the local anesthetic. Psychogenic reactions to injections may be misdiagnosed as allergic reactions and may also mimic them with signs such as urticaria, edema, and bronchospasm. True allergy to an amide local anesthetic is exceedingly rare, whereas the ester procaine is somewhat more allergenic. Allergy to one ester rules out use of another ester, because the allergenic component is the metabolite para-aminobenzoic acid (PABA), produced by all esters. In contrast, allergy to one amide does not rule out the use of another

amide. A patient may be allergic to other compounds in the local anesthetic, such as preservatives in multidose vials.

- E. **Administration to children and the elderly:** Before administering local anesthetic to a child, the maximum dose based on weight should be calculated to prevent accidental overdose. There are no significant differences in response to local anesthetics between younger and older adults. It is prudent to stay well below maximum recommended doses in elderly patients who often have some compromise in liver function. Because some degree of cardiovascular compromise may be expected in elderly patients, reducing the dose of epinephrine may be prudent.
- F. **Systemic local anesthetic toxicity:** Toxic blood levels of the drug may be due to repeated injections or could result from a single inadvertent IV injection. Aspiration before every injection is imperative. The signs, symptoms, and timing of local anesthetic systemic toxicity are unpredictable. One must consider the diagnosis in any patient with altered mental status or cardiovascular instability following injection of local anesthetic. CNS symptoms (either excitation or depression) may be apparent but may also be subtle, nonspecific, or absent. Treatment for systemic local anesthetic toxicity includes airway management, support of breathing and circulation, seizure suppression and, if needed, cardiopulmonary resuscitation.

Characteristic	Esters	Amides
	Procaine Chloroprocaine Tetracaine Cocaine	Lidocaine, Bupivacaine Ropivacaine, Mepivacaine Prilocaine
Metabolism	Rapid by plasma cholinesterase	Slow, hepatic
Systemic toxicity	Less likely	More likely
Allergic reaction	Possible- PABA derivatives form	Very rare
Stability in solution	Breaks down in ampules (heat, sun)	Very stable chemically
Onset of action	Slow as a general rule	Moderate to fast

Differences between esters and amides of local anesthetics

Drug	Potency	Onset	Duration
Procaine	Low	Rapid	Short
Chloroprocaine	Low	Rapid	Short
Tetracaine	High	Slow	Long (spinal)
Lidocaine	Low	Rapid	Intermediate
Mepivacaine	Low	Moderate	Intermediate
Bupivacaine	High	Slow	Long
Ropivacaine	High	Moderate	Long

Summary of pharmacologic properties of some local anesthetics.





Department of Dentistry

Pharmacology

2022-2023

Lecturer

Faris E. Mohammed

Lecture 12

Anxiolytics and Sedative

Anxiety is an unpleasant state of tension, apprehension, or uneasiness (a fear that arises from either a known or an unknown source). The physical symptoms of severe anxiety are similar to those of fear (such as tachycardia, sweating, trembling, and palpitations) and involve sympathetic activation.

Because many antianxiety drugs also cause some sedation, they may be used clinically as both anxiolytic and hypnotic (sleep inducing) agents.

Benzodiazepines:

Benzodiazepines are widely used anxiolytic drugs. They have largely replaced barbiturates and meprobamate in the treatment of anxiety and insomnia, because benzodiazepines are generally considered to be safer and more effective (Alprazolam, Clonazepam, Clorazepate, Diazepam, Lorazepam).

Mechanism of action:

Benzodiazepine bind and activate the γ -aminobutyric acid (GABA_A) receptors, triggers an opening of the chloride channel, the influx of chloride ions causes hyperpolarization of the neuron and decreases neurotransmission by inhibiting the formation of action potentials.

Action:

1. Reduction of anxiety (At low doses).
2. Sedative/hypnotic (high dose).
3. Centrally muscle relaxant.

Adverse effects:

- a. Benzodiazepines should be used cautiously in patients with liver disease.
- b. Drowsiness and confusion.
- c. Ataxia.
- d. Cognitive impairment.
- e. Tolerance.
- f. Effect on oral and dental structure: Xerostomia.

Drug interaction:

- Enhancements of other CNS inhibitors (alcohol).
- Decreased serum concentration with carbamazepine (enzyme inducer).
- Decreased serum concentration with erythromycin, ketoconazole (enzyme inhibitors).

Benzodiazepine Antagonist:

Flumazenil is a GABA receptor antagonist that can rapidly reverse the effects of benzodiazepines.

Other anxiolytic agents

A. **Antidepressants:** Many antidepressants are effective in the treatment of chronic anxiety disorders and should be considered as first-line agents, especially in patients with concerns for addiction or dependence.

1. **Selective serotonin reuptake inhibitors (SSRIs):** Escitalopram or paroxetine.
2. **Serotonin/norepinephrine reuptake inhibitors (SNRIs):** such as venlafaxine or duloxetine.

May be used alone or prescribed in combination with a low dose of a benzodiazepine during the first weeks of treatment. After 4 to 6 weeks, when the antidepressant begins to produce an anxiolytic effect, the benzodiazepine dose can be tapered. SSRIs and SNRIs have a lower potential for physical dependence than the benzodiazepines.

B. Buspirone:

Buspirone is useful for the chronic treatment of anxiety.

It has a slow onset of action and is not effective for short-term or “as-needed” treatment of acute anxiety states. The actions of buspirone appear to be mediated by serotonin (5-HT_{1A}) receptors agonist that increase the effects of serotonin to overcome anxiety.

Thus, its mode of action differs from that of the benzodiazepines. In addition, buspirone lacks the anticonvulsant and muscle-relaxant properties of the benzodiazepines.

Adverse effects:

Xerostomia, headaches, dizziness, nervousness, nausea, and light-headedness. Sedation and psychomotor and cognitive dysfunction are minimal.

Drug interaction:

Increase CNS depression occurs with alcohol and other CNS depressant.





Department of Dentistry

Pharmacology

2022-2023

Lecturer

Faris E. Mohammed

Lecture 13

Diabetes Mellitus:

The pancreas produces the peptide hormones insulin, glucagon, and somatostatin. The peptide hormones are secreted from cells in the islets of Langerhans (β cells produce insulin, α cells produce glucagon, and δ cells produce somatostatin). These hormones play an important role in regulating metabolic activities of the body, particularly glucose homeostasis. A relative or absolute lack of insulin, as seen in diabetes mellitus, can cause serious hyperglycemia. Left untreated, retinopathy, nephropathy, neuropathy, and cardiovascular complications may result. Administration of insulin preparations or other glucose-lowering agents can reduce morbidity and mortality associated with diabetes

The American Diabetes Association (ADA) recognizes four clinical classifications of diabetes: type 1 diabetes (formerly insulin-dependent diabetes mellitus), type 2 diabetes (formerly non– insulin-dependent diabetes mellitus), gestational diabetes, and diabetes due to other causes such as genetic defects or medications.

Type 1 diabetes

Type 1 diabetes most commonly afflicts children, adolescents, or young adults, but some latent forms occur later in life. The disease is characterized by an absolute deficiency of insulin due to destruction of β cells. Loss of β -cell function results from autoimmune-mediated processes that may be triggered by viruses or other environmental toxins.

Without functional β cells, the pancreas fails to respond to glucose, and a person with type 1 diabetes shows classic symptoms of insulin deficiency (polydipsia, polyphagia, polyuria, and weight loss). Type 1 diabetics require exogenous insulin to avoid severe hyperglycemia and the life-threatening catabolic state of ketoacidosis.

INSULIN

Insulin is a polypeptide hormone consisting of two peptide chains that are connected by disulfide bonds.

Pharmacokinetics:

Human insulin is produced by recombinant DNA technology using strains of *Escherichia coli* or yeast that are genetically altered to contain the gene for human insulin

Because insulin is a polypeptide, it is degraded in the gastrointestinal tract if taken orally. Therefore, it is generally administered by subcutaneous injection. [Note: In a hyperglycemic emergency, regular insulin is administered intravenously (IV).] Continuous subcutaneous insulin infusion (also called the insulin pump) is another method of insulin delivery.

Adverse reactions:

Hypoglycemia is the most serious and common adverse reaction to insulin.

Other adverse reactions include weight gain, local injection site reactions, and lipodystrophy. Lipodystrophy can be minimized by rotation of injection sites. Diabetics with renal insufficiency may require a decrease in insulin dose

INSULIN PREPARATIONS

A. Rapid-acting and short-acting insulin

Preparations (**regular insulin**, **insulin lispro**, **insulin aspart**.) Modification of the amino acid sequence of regular insulin produces analogs that are rapid-acting insulins. For example, insulin lispro differs from regular insulin in that the lysine and proline at positions 28 and 29 in the B chain are reversed. Regular insulin should be injected subcutaneously 30 minutes before a meal, whereas rapid-acting insulins are administered in the 15 minutes preceding a meal or within 15 to 20 minutes after starting a meal.

B. Intermediate-acting insulin (NPH)

Delayed absorption and a longer duration of action (**insulin isophane**)

C. Long-acting insulin preparations

The isoelectric point of (**insulin glargine**) is lower than that of human insulin, leading to formation of a precipitate at the injection site that releases insulin over an extended period.

D. Insulin combinations Various premixed combinations of human insulins, such as **70% NPH insulin** plus **30% regular insulin** or 50% of each of these are also available.

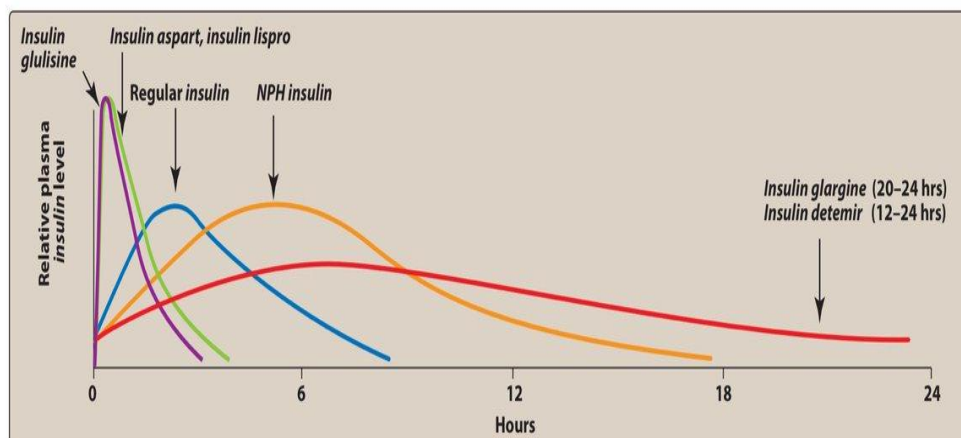
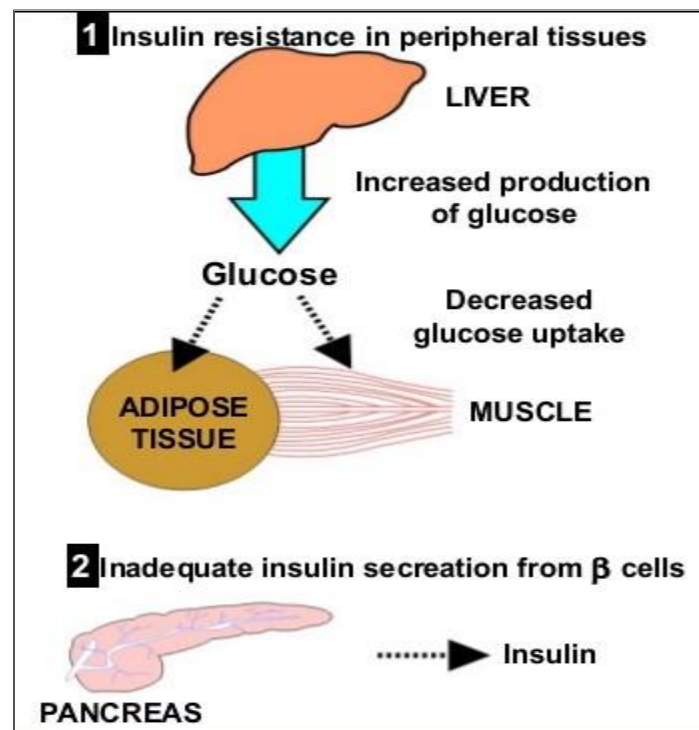


Figure 24.7

Onset and duration of action of human *insulin* and insulin analogs. NPH = neutral protamine Hagedorn.

Type 2 diabetes

Is characterized by a lack of sensitivity of target organs to insulin, In type 2 diabetes, the pancreas retains some β -cell function, but insulin secretion is insufficient to maintain glucose homeostasis, in the face of increasing peripheral insulin resistance. The β -cell mass may gradually decline over time in type 2 diabetes. In contrast to patients with type 1, those with type 2 diabetes are often obese. Obesity contributes to insulin resistance, which is considered the major underlying defect of type 2 diabetes.



Treatment:

The goal in treating type 2 diabetes is to maintain blood glucose within normal limits and to prevent the development of long-term complications. Weight reduction, exercise, and dietary modification decrease insulin resistance and correct hyperglycemia in some

patients with type 2 diabetes. However, most patients require pharmacologic intervention with oral glucose-lowering agents. As the disease progresses, β -cell function declines and insulin therapy is often needed to achieve satisfactory glu. levels.

Oral hypoglycaemic drugs

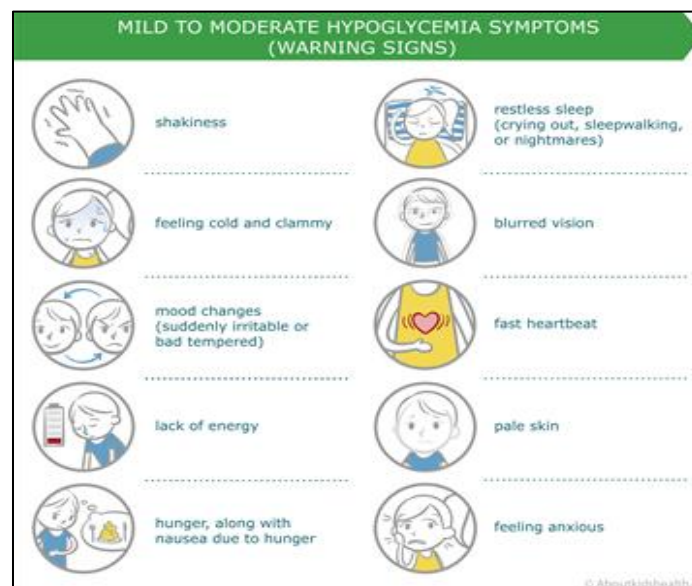
Sulfonylureas (**glibenclamide**) these agents are classified as insulin secretagogues, because they promote insulin release from the β cells of the pancreas.

Mechanism of action:

The main mechanism of action includes stimulation of insulin release from the β cells of the pancreas. Sulfonylureas block ATP-sensitive K^+ channels, resulting in depolarization, Ca^{2+} influx, and insulin exocytosis. In addition, sulfonylureas may reduce hepatic glucose production and increase peripheral insulin sensitivity.

Adverse effects:

Major adverse effects of the sulfonylureas are weight gain, hyperinsulinemia, and hypoglycemia



Oral manifestation:

Oro_facial neuropathy (tingling or burning in the lips and tongue).

Drug interaction:

1. Enhance hypoglycemic action(aspirin, NSAIDs).
2. Increase plasma concentration of glibenclamide (fluconazole, miconazole).
3. Antagonize hypoglycaemic properties of glibenclamide (systemic corticosteroids).

Biguanides (Metformin)

The main mechanism of action of metformin is reduction of hepatic gluconeogenesis. [Note: Excess glucose produced by the liver is a major source of high blood glucose in type 2 diabetes, accounting for high fasting blood glucose.] Metformin also slows intestinal absorption of sugars and improves peripheral glucose uptake and utilization. Weight loss may occur because metformin causes loss of appetite

Adverse effects:

These are largely gastrointestinal. Metformin is contraindicated in renal dysfunction due to the risk of lactic acidosis.

Other uses:

In addition to type 2 diabetes, metformin is effective in the treatment of polycystic ovary syndrome. It lowers insulin resistance seen in this disorder and can result in ovulation and, therefore, possibly pregnancy.

Oral manifestation: metformin cause metallic taste in mouth.

Drug interaction: systemic corticosteroid antagonize the hypoglycemic action of metformin.





Department of Dentistry

Pharmacology

2022-2023

Lecturer

Faris E. Mohammed

Lecture (14)

Anticoagulants

The anticoagulant drugs inhibit either the action of the coagulation factors (for example, heparin) or interfere with the synthesis of the coagulation factors (for example, vitamin K antagonists such as warfarin).

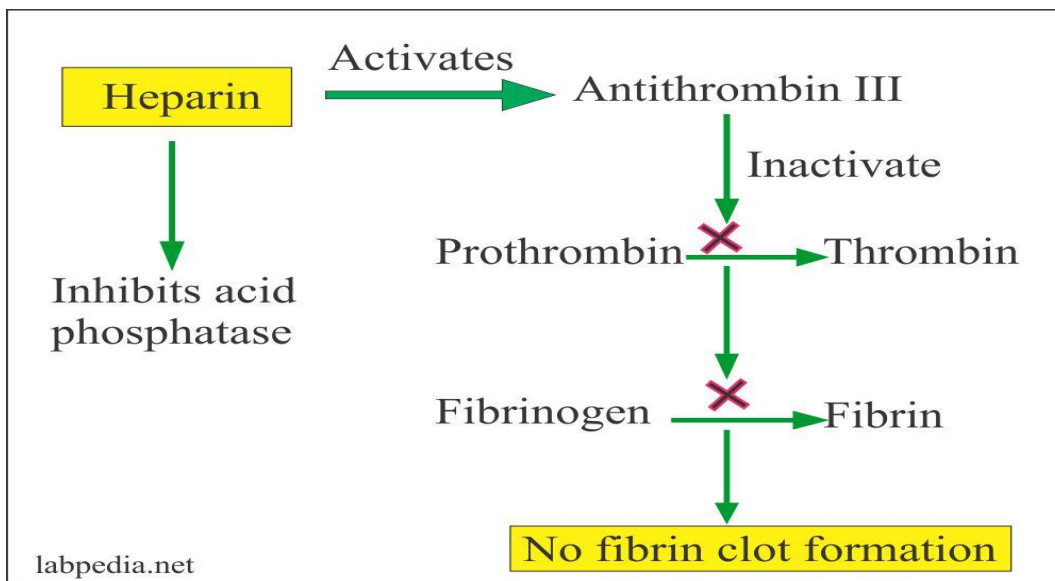
A. Heparin and low molecular weight heparins:

Heparin is an injectable, rapidly acting anticoagulant that is often used acutely to interfere with the formation of thrombi. Heparin occurs naturally as a macromolecule complexed with histamine in mast cells, where its physiologic role is unknown. It is extracted for commercial use from porcine intestinal mucosa and bovine lung. It is strongly acidic because of the presence of sulfate and carboxylic acid groups. The realization that low molecular weight forms of heparin (LMWHs) can also act as anticoagulants led to the isolation of enoxaparin, produced by enzymatic depolymerization of unfractionated heparin. Other LMWHs include dalteparin and tinzaparin. The LMWHs are heterogeneous compounds about one-third the size of unfractionated heparin.

Mechanism of action:

Heparin acts at a number of molecular targets, but its anticoagulant effect is a consequence of binding to antithrombin III, with the subsequent rapid inactivation of coagulation factors. Antithrombin III is an α globulin that inhibits serine proteases of thrombin (factor IIa) and factor Xa.

In the absence of heparin, antithrombin III interacts very slowly with thrombin and factor Xa. When heparin molecules bind to antithrombin III, a conformational change occurs that catalyzes the inhibition of thrombin about 1000-fold.



Pharmacokinetics:

Heparin must be administered subcutaneously or intravenously, because the drug does not readily cross membranes. The LMWHs are administered subcutaneously.

Heparin is often initiated as an intravenous bolus to achieve immediate anticoagulation. This is followed by lower doses or continuous infusion of heparin, titrating the dose so that the activated partial thromboplastin time (aPTT) is 1.5- to 2.5-fold that of the normal control.

Adverse effects:

- a. Bleeding.
- b. Thrombocytopenia.
- c. Osteoporosis.

Contraindicated:

Heparin and LMWHs are contraindicated in patients who have hypersensitivity to heparin, bleeding disorders, alcoholism, or who have had recent surgery of the brain, eye, or spinal cord.

Oral and dental effects: no direct effect although patient with long use heparin are susceptible to osteoporosis and perhaps periodontal breakdown

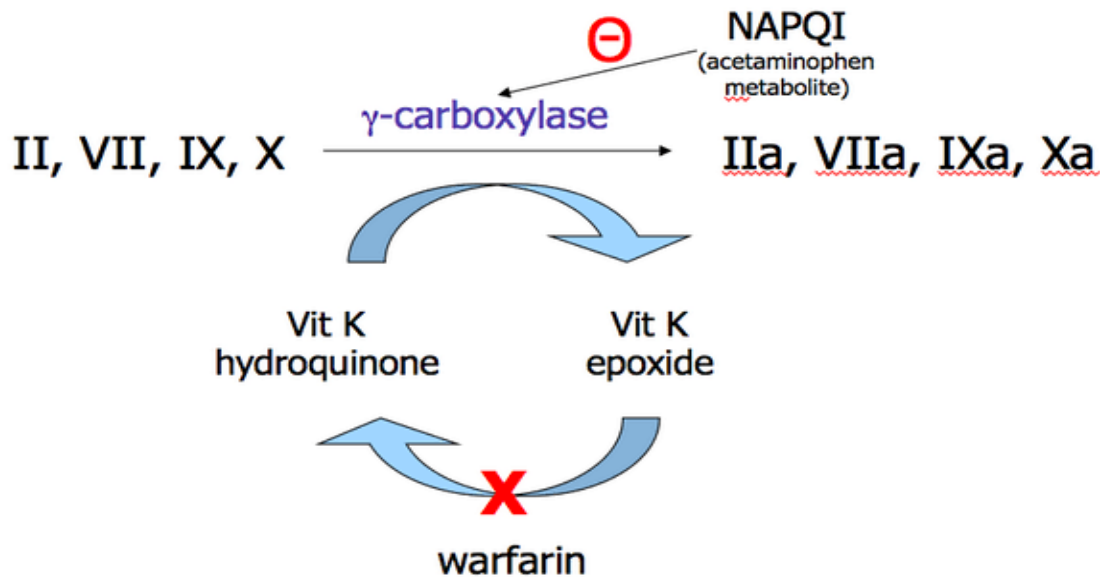
Warfarin:

The coumarin anticoagulants owe their action to the ability to antagonize the cofactor functions of vitamin K. The only therapeutically relevant coumarin anticoagulant is warfarin. Initially used as a rodenticide, warfarin is now widely used clinically as an oral anticoagulant.

The international normalized ratio blood test (INR) or Prothrombin time (PT) is the standard by which the anticoagulant activity of warfarin therapy is monitored. The goal of warfarin therapy is an INR of 2 to 3 for most indications, with an INR of 2.5 to 3.5 targeted for some mechanical valves and other indications. Warfarin has a narrow therapeutic index. Therefore, it is important that the INR is maintained within the optimal range as much as possible, and frequent monitoring may be required.

Mechanism of action:

Factors II, VII, IX, and X require vitamin K as a cofactor for their synthesis by the liver. Warfarin antagonize the cofactor functions of vitamin K.



Therapeutic use:

Warfarin is used in the prevention and treatment of DVT and PE, stroke prevention, stroke prevention in the setting of atrial fibrillation and/or prosthetic heart valves. It is also used for prevention of venous thromboembolism during orthopedic or gynecologic surgery.

Adverse effects:

The principal adverse effect of warfarin is hemorrhage, and the agent has a black box warning for bleeding risk. Therefore, it is important to frequently monitor the INR and adjust the dose of warfarin. Minor bleeding may be treated by withdrawal of the drug or administration of oral vitamin K1, but severe bleeding may require greater doses of vitamin K given intravenously. Whole blood, frozen plasma, and plasma concentrates of blood factors may also be used for rapid reversal of warfarin. Skin lesions and necrosis

are rare complications of warfarin therapy. Warfarin is teratogenic and should never be used during pregnancy. If anticoagulant therapy is needed during pregnancy, heparin or LMWH may be administered.

Pharmacokinetics:

Warfarin is metabolized by the CYP450 system (including the 2C9, 2C19, 2C8, 2C18, 1A2, and 3A4 isoenzymes) to inactive components. After conjugation to glucuronic acid, the inactive metabolites are excreted in urine and feces. Agents that affect the metabolism of warfarin may alter its therapeutic effects. Warfarin has numerous drug interactions that may potentiate or attenuate its anticoagulant effect.

Drug interaction:

- a. Potentiation of anticoagulant effect (ciprofloxacin, erythromycin, azithromycin [6 case reports] metronidazole, fluconazole, Sulfamethoxazole/ Trimethoprim) Inhibition of metabolism of warfarin.
- b. Attenuation of anticoagulant effect (Barbiturates, Rifampin) Stimulation of metabolism of warfarin.
 - We can give alternative drug that not interact with warfarin.

Dental managements:

Uncomplicated Oral surgery can be done depend on INR (1.5-2.5). Stop warfarin 2-3 day before the procedure.





Department of Dentistry

Pharmacology

2022-2023

Lecturer

Faris E. Mohammed

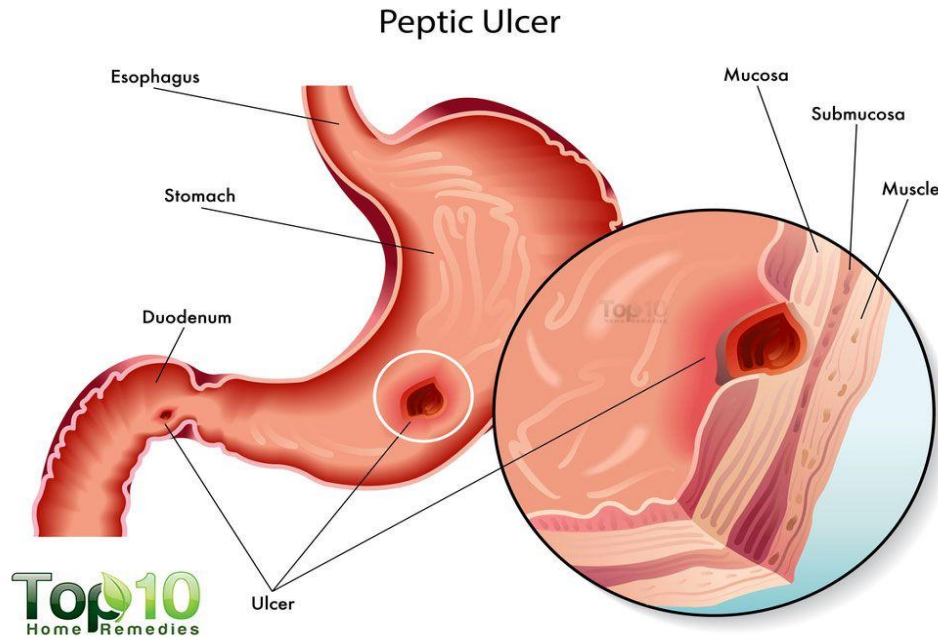
Lec 15

Gastro Intestinal disorder

Peptic ulcer

Peptic ulcers are sores that develop in the lining of the stomach, lower esophagus, or small intestine. They're usually formed as a result of inflammation caused by the bacteria *H. pylori*, as well as from erosion from stomach acids.

The two main causes of peptic ulcer disease are infection with gram-negative *Helicobacter pylori* and the use of nonsteroidal anti-inflammatory drugs (NSAIDs). Increased hydrochloric acid (HCl) secretion and inadequate mucosal defense against gastric acid also play a role.



Treatment approaches include

- 1- Eradicating the *H. pylori* infection.
- 2- Reducing secretion of gastric acid with the use of PPIs or H₂-receptor antagonists, and/or
- 3- Providing agents that protect the gastric mucosa from damage, such as misoprostol

Reducing secretion of gastric acid.

Gastric acid secretion is stimulated by acetylcholine, histamine, and gastrin. The receptor-mediated binding of acetylcholine, histamine, or gastrin results in the activation of protein kinases, which in turn stimulates the H⁺/K⁺-adenosine triphosphatase (ATPase) proton pump to secrete hydrogen ions in exchange for K⁺ into the lumen of the stomach. By competitively blocking the binding of histamine to H₂ receptors, these agents reduce the secretion of gastric acid. The four drugs used in the United States—cimetidine, ranitidine, famotidine and nizatidine, potently inhibit (greater than 90%)

basal, food-stimulated, and nocturnal secretion of gastric acid. Cimetidine was the first histamine H₂-receptor antagonist.

Actions:

The histamine H₂-receptor antagonists act selectively on H₂ receptors in the stomach, but they have no effect on H₁ receptors. They are competitive antagonists of histamine and are fully reversible.

Uses:

1- Peptic ulcers

2- Acute stress ulcers

3- Gastroesophageal reflux disease

Adverse effects:

In general, the H₂ antagonists are well tolerated. Cimetidine can have endocrine effects because it acts as a nonsteroidal antiandrogen. These effects include gynecomastia and galactorrhea (continuous release/discharge of milk). Other central nervous system effects (such as confusion and altered mentation) occur primarily in elderly patients and after intravenous administration. Cimetidine inhibits several cytochrome P450 isoenzymes and can interfere with the metabolism of many other drugs, such as warfarin, phenytoin, and clopidogrel. All H₂ antagonists may reduce the efficacy of drugs that require an acidic environment for absorption, such as ketoconazole.

Proton pump inhibitor PPIs:

The PPIs bind to the H⁺/K⁺-ATPase enzyme system (proton pump) and suppress the secretion of hydrogen ions into the gastric lumen. The membrane-bound proton pump is the final step in the secretion of gastric acid. The available PPIs include esomeprazole, lansoprazole, omeprazole, pantoprazole, and rabeprazole.

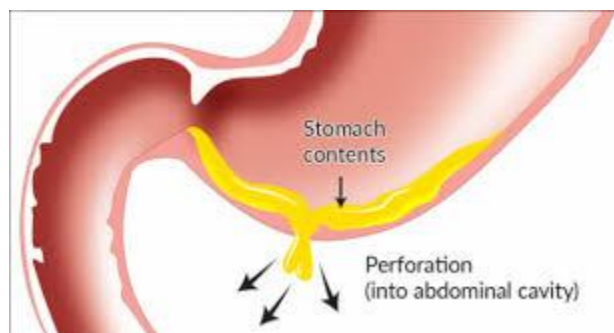
Adverse effects: The PPIs are generally well tolerated. Omeprazole and esomeprazole may decrease the effectiveness of clopidogrel because they inhibit CYP2C19 and

prevent the conversion of clopidogrel to its active metabolite. Prolonged acid suppression with PPIs (and H₂ antagonists) may result in low vitamin B₁₂ because acid is required for its absorption in a complex with intrinsic factor.

Prostaglandins Prostaglandin E

Produced by the gastric mucosa, inhibits secretion of acid and stimulates secretion of mucus and bicarbonate (cytoprotective effect). A deficiency of prostaglandins is thought to be involved in the pathogenesis of peptic ulcers. Misoprostol an analog of prostaglandin E₁, is approved for the prevention of NSAID-induced gastric ulcers. Prophylactic use of misoprostol should be considered in patients who are taking NSAIDs and are at moderate to high risk of NSAID-induced ulcers, such as elderly patients and those with previous ulcers.

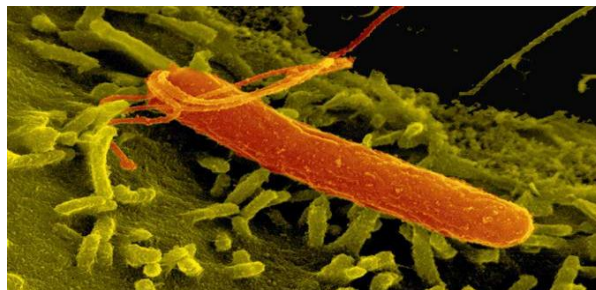
Misoprostol is contraindicated in pregnancy, since it can stimulate uterine contractions and cause miscarriage. Dose-related diarrhea and nausea are the most common adverse effects and limit the use of this agent. Thus, PPIs are preferred agents for the prevention of NSAID-induced ulcers.



H. pylori

Patients with peptic ulcer disease (duodenal or gastric ulcers) who are infected with H. pylori require antimicrobial treatment. Eradication of H. pylori results in rapid healing of active ulcers and low recurrence rates (less than 15% compared with 60% to 100% per year for initial ulcers healed with acid-reducing therapy alone). Successful eradication of H. pylori (80% to 90%) is possible with various combinations of antimicrobial drugs.

Currently, triple therapy consisting of a PPI combined with amoxicillin and metronidazole (clarithromycin may be used in penicillin-allergic patients) is the therapy of choice.



Antacids Antacids

are weak bases that react with gastric acid to form water and a salt to diminish gastric acidity. Because pepsin (a proteolytic enzyme) is inactive at a pH greater than 4, antacids also reduce pepsin activity.

Adverse effects:

Aluminum hydroxide tends to cause constipation, whereas magnesium hydroxide tends to produce diarrhea. Preparations that combine these agents aid in normalizing bowel function. Absorption of the cations from antacids (Mg^{2+} , Al^{3+} , Ca^{2+}) is usually not a problem in patients with normal renal function; however, accumulation and adverse effects may occur in patients with renal impairment.

Mucosal protective agents

Also known as cytoprotective compounds, these agents have several actions that enhance mucosal protection mechanisms, thereby preventing mucosal injury, reducing inflammation, and healing existing ulcers.

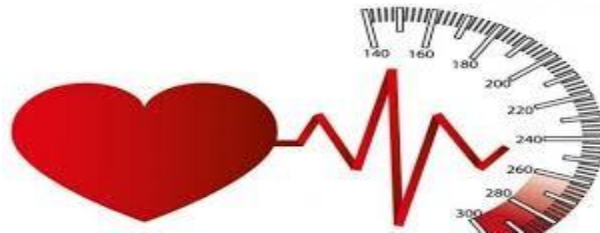
1. Sucralfate:

This complex of aluminum hydroxide and sulfated sucrose binds to positively charged groups in proteins of both normal and necrotic mucosa. By forming complex gels with

epithelial cells, sucralfate creates a physical barrier that protects the ulcer from pepsin and acid, allowing the ulcer to heal. Sucralfate is well tolerated, but it can interfere with the absorption of other drugs by binding to them. Although sucralfate is effective for the treatment of duodenal ulcers and prevention of stress ulcers, its use is limited due to the need for multiple daily dosing and drug–drug interactions. Because it requires an acidic pH for activation, sucralfate should not be administered with PPIs, H₂ antagonists, or antacids. This agent does not prevent NSAID-induced ulcers, and it does not heal gastric ulcers.

2. Bismuth subsalicylate:

This agent is used as a component of quadruple therapy to heal peptic ulcers. In addition to its antimicrobial actions, it inhibits the activity of pepsin, increases secretion of mucus, and interacts with glycoproteins in necrotic mucosal tissue to coat and protect the ulcer.





Department of Dentistry

Pharmacology

2022-2023

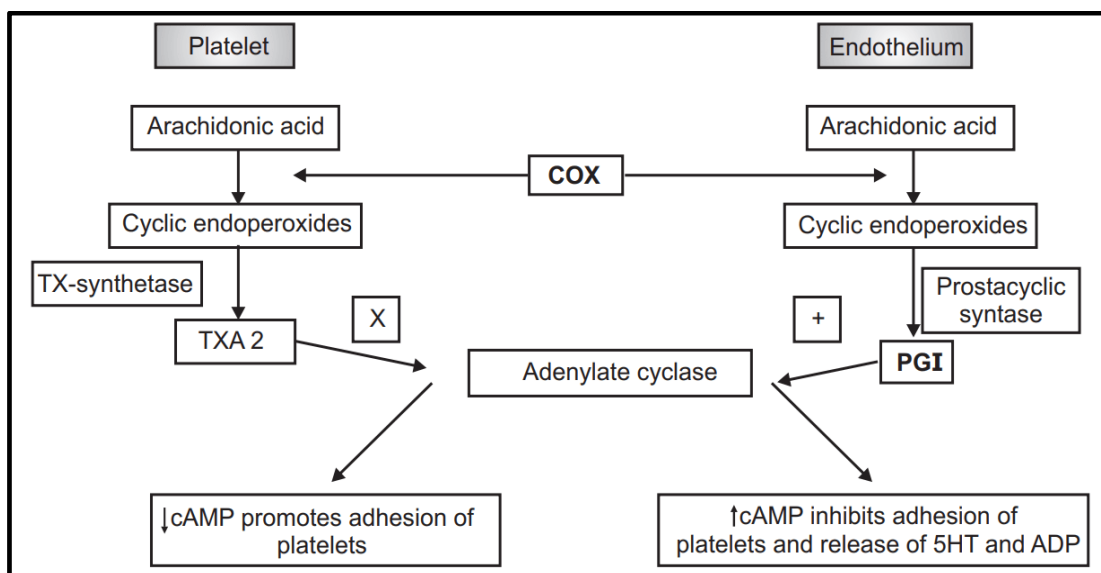
Lecturer

Faris E. Mohammed

Lecture (16)

Anti-platelets

Platelet aggregation inhibitors decrease the formation of a platelet-rich clot or decrease the action of chemical signals that promote platelet aggregation. Because these agents have different mechanisms of actions, synergistic or additive effects may be achieved when agents from different classes are combined. These agents are beneficial in the prevention and treatment of occlusive cardiovascular diseases.



Aspirin:

Mechanism of action: Stimulation of platelets by thrombin, collagen, and ADP results in activation of platelet membrane phospholipases that liberate arachidonic acid from membrane phospholipids.

Arachidonic acid is first converted to prostaglandin H₂ by COX-1

Prostaglandin H₂ is further metabolized to thromboxane A₂, which is released into plasma.

Thromboxane A₂ promotes the aggregation process that is essential for the rapid formation of a hemostatic plug. Aspirin inhibits thromboxane A₂ synthesis by acetylation of a serine residue on the active site of COX-1, thereby irreversibly inactivating the enzyme.

This shifts the balance of chemical mediators to favor the antiaggregatory effects of prostacyclin, thereby preventing platelet aggregation.

Therapeutic use:

Aspirin is used in the prophylactic treatment of transient cerebral ischemia, to reduce the incidence of recurrent MI, and to decrease mortality in the setting of primary and secondary prevention of MI.

Complete inactivation of platelets occurs with 75 mg of aspirin given daily. The recommended dose of aspirin ranges from 50 to 325 mg daily.

Adverse effects:

increased incidence of hemorrhagic stroke and gastrointestinal (GI) bleeding, especially at higher doses of the drug.

Ticlopidine, clopidogrel, prasugrel and ticagrelor:

Mechanism of action:

These drugs inhibit the binding of ADP to its receptors on platelets and, thereby, inhibit the activation of the GP IIb/IIIa receptors required for platelets to bind to fibrinogen and to each other.

Adverse effects:

These agents can cause prolonged bleeding for which there is no antidote. Ticlopidine is associated with severe hematologic reactions that limit its use, such as agranulocytosis, thrombotic thrombocytopenic purpura (TTP), and aplastic anemia. Clopidogrel causes fewer adverse reactions, and the incidence of neutropenia is lower.

Dipyridamole:

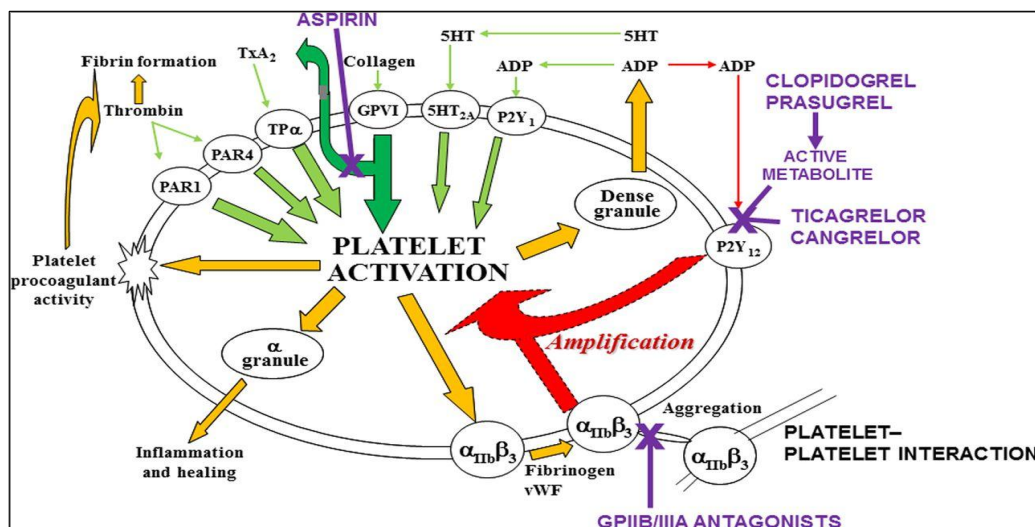
Coronary vasodilator, increases intracellular levels of cAMP by inhibiting cyclic nucleotide phosphodiesterase, thereby resulting in decreased thromboxane A₂ synthesis. The drug may potentiate

the effect of prostacyclin to antagonize platelet stickiness and, therefore, decrease platelet adhesion to thrombogenic surfaces. Dipyridamole is used for stroke prevention and is usually given in combination with aspirin. Dipyridamole has variable bioavailability following oral administration. It is highly protein bound . The drug undergoes hepatic metabolism, as well as glucuronidation, and is excreted mainly in the feces. Patients with unstable angina should not use dipyridamole because of its vasodilating properties, which may worsen ischemia (coronary steal phenomenon).

Dipyridamole commonly causes headache and can lead to orthostatic hypotension (especially if administered IV).

Cilostazol:

is an oral antiplatelet agent that also has vasodilating activity. Cilostazol and its active metabolites inhibit phosphodiesterase type III, which prevents the degradation of cAMP, thereby increasing levels of cAMP in platelets and vascular tissues. The increase in cAMP levels in platelets and the vasculature prevents platelet aggregation and promotes vasodilation of blood vessels, respectively.





Department of Anesthesia

Pharmacology

2022-2023

Lecturer

Faris E. Mohammed

Lecture 17

Epilepsy

Epilepsy is not a single entity but an assortment of different seizure types and syndromes originating from several mechanisms that have in common the sudden, excessive, and synchronous discharge of cerebral neurons. This abnormal electrical activity may result in a variety of events, including loss of consciousness, abnormal movements, atypical or odd behavior, and distorted perceptions that are of limited duration but recur if untreated.

Antiepileptic medication:

Mechanism of action of antiepilepsy medications

- Reduce seizures through such mechanisms as blocking voltage-gated channels (Na^+ or Ca^{2+}).
- Enhancing inhibitory γ -aminobutyric acid (GABA)-ergic impulses.

- Interfering with excitatory glutamate transmission.

Antiepilepsy medications suppress seizures but do not “cure” or “prevent” epilepsy.

Antiepilepsy medication:

A. Benzodiazepines:

Benzodiazepines bind to GABA inhibitory receptors to reduce firing rate. Most benzodiazepines are reserved for emergency or acute seizure treatment due to tolerance. However, clonazepam and clobazam may be prescribed as adjunctive therapy for particular types of seizures. Diazepam is also available for rectal administration to avoid or interrupt prolonged generalized tonic-clonic seizures or clusters when oral administration is not possible.

B. Carbamazepine:

Carbamazepine blocks sodium channels, thereby inhibiting the generation of repetitive action potentials in the epileptic focus and preventing their spread. Carbamazepine is effective for treatment of focal seizures and, additionally generalized tonic-clonic seizures, trigeminal neuralgia, and bipolar disorder. Carbamazepine is absorbed slowly and erratically following oral administration and may vary from generic to generic, resulting in large variations in serum concentrations of the drug. It induces its own metabolism, resulting in lower total carbamazepine blood concentrations at higher doses.

Adverse Effect:

Carbamazepine is an inducer of the CYP1A2, CYP2C, and CYP3A and UDP glucuronosyltransferase (UGT) enzymes in the liver, which increases the clearance of other drugs. (warfarin, oral contraceptive)

- C. **Gabapentin**: Gabapentin is an analog of GABA. However, it does not act at GABA receptors, enhance GABA actions or convert to GABA. Its precise mechanism of action is not known. It is approved as adjunct therapy for focal seizures and treatment of postherpetic neuralgia .
- D. **Pregabalin**: binds to the $\alpha 2\text{-}\delta$ site, an auxiliary subunit of voltage-gated calcium channels in the CNS, inhibiting excitatory neurotransmitter release. The exact role this plays in treatment is not known, but the drug has proven effects on focal-onset seizures, diabetic peripheral neuropathy, postherpetic neuralgia, and fibromyalgia. More than 90% of pregabalin is eliminated renally. Dosage adjustments are needed in renal dysfunction. It has no significant metabolism and few drug interactions. Weight gain and peripheral edema have been reported.
- E. **Lamotrigine**: Lamotrigine blocks sodium channels, as well as high voltage-dependent calcium channels. Lamotrigine is effective in a wide variety of seizure types, including focal, generalized, absence seizures.
- F. **Phenytoin**: Blocks voltage-gated sodium channels by selectively binding to the channel in the inactive state and slowing its rate of recovery.

Adverse effect: Gum hyperplasia.

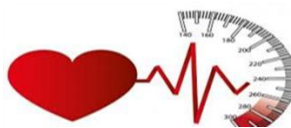
Phenobarbital and primidone.

The primary mechanism of action of phenobarbital [fee-noe-BARbih- tal] is enhancement of the inhibitory effects of GABA-mediated neurons (see Chapter 9). Primidone is metabolized to phenobarbital (major) and phenylethylmalonamide, both with anticonvulsant activity. Phenobarbital is used primarily in the treatment of status epilepticus when other agents fail.

Topiramate: has multiple mechanisms of action. It blocks voltage-dependent sodium channels, reduces high-voltage calcium currents (L type), is a carbonic anhydrase inhibitor, and may act at glutamate (NMDA) sites. Topiramate is effective for use in partial and primary generalized epilepsy. It is also approved for prevention of migraine. It inhibits CYP2C19 and is induced by phenytoin and carbamazepine. Adverse effects include somnolence, weight loss, and paresthesias. Renal stones, glaucoma, oligohidrosis (decreased sweating), and hyperthermia have also been reported.

G. **Valproic acid:** mechanisms of action include sodium channel blockade, blockade of GABA transaminase, and action at the T-type calcium channels. These varied mechanisms provide a broad spectrum of activity against seizures. Valproate inhibits metabolism of the CYP2C9, UGT, and epoxide hydrolase systems. Rare hepatotoxicity may cause a rise in liver enzymes, which should be monitored frequently. Teratogenicity is also of great concern.

Pregnancy: Several antiepilepsy medications increase the metabolism of hormonal contraceptives, potentially rendering them ineffective. These include phenytoin, phenobarbital, carbamazepine, topiramate, oxcarbazepine, rufinamide, and clobazam. These medications increase the metabolism of contraceptives regardless of the delivery system used (for example, patch, ring, implants, and oral tablets). Pregnancy planning is vital, as many antiepilepsy medications have the potential to affect fetal development and cause birth defects. All women considering pregnancy should be on high doses (1 to 5 mg) of folic acid prior to conception.





Department of Dentistry

Pharmacology

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Lecturer

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Lecture 18

Antipsychotic Drugs

Schizophrenia

Schizophrenia is a type of chronic psychosis characterized by delusions, hallucinations (often in the form of voices), and thinking or speech disturbances. The onset of illness is often during late adolescence or early adulthood. It occurs in about 1% of the population and is a chronic and disabling disorder. Schizophrenia has a strong genetic component and probably reflects some fundamental biochemical abnormality, possibly a **dysfunction of the mesolimbic or mesocortical dopaminergic neuronal pathways.**

Note:

Extrapyramidal effects: Dystonias (sustained contraction of muscles leading to twisting, distorted postures), Parkinson-like symptoms, akathisia (motor restlessness), and tardive

dyskinesia (involuntary movements, usually of the tongue, lips, neck, trunk, and limbs) can occur with both acute and chronic treatment. Blockade of dopamine receptors in the nigrostriatal pathway probably causes these unwanted movement symptoms. The second generation antipsychotics exhibit a lower incidence of EPS.

The antipsychotic drugs are divided into **first-** and **second-**generation agents, this classification indicate specifies affinity for the dopamine D₂ receptor, which, in turn, may influence the adverse effect profile of the drug.

A. First generation agents (typical):

All of the first-generation drugs **block D2 dopamine receptors** in the brain and the periphery. First-generation antipsychotics are more likely to be associated with movement disorders known as extrapyramidal symptoms (EPS), particularly drugs that bind tightly to dopaminergic neuroreceptors (haloperidol, chlorpromazine).

B. Second generation agents (atypical):

1. Block D₂ dopamine receptors in the brain and the periphery
2. Most of the second generation agents appear to exert part of their unique action through inhibition of serotonin receptors (5-HT).

They have a lower incidence of (EPS) than the first- generation agents but are associated with a higher risk of metabolic side effects, such as diabetes, hypercholesterolemia, and weight gain (Clozapine, olanzapine, Risperidone).

Therapeutic effects:

All antipsychotic drugs can reduce hallucinations and delusions associated with schizophrenia (known as “positive” symptoms) by blocking D2 receptors in the mesolimbic system of the brain. The “negative” symptoms, such as blunted affect, apathy, and impaired attention, as well as cognitive impairment, are not as responsive to therapy, particularly with

the first-generation antipsychotics. Many second-generation agents, such as clozapine, can ameliorate the negative symptoms to some extent.

Titles	1 st generation antipsych. (Haloperidol, chlorpromazine).	2 nd generation antipsych. (Clozapine, olanzapine)
Name	typical	atypical
Mechanism of action	blocking of dopamine D2 receptors	Blockade serotonin and dopamine D ₂ receptors
Therapeutic uses	Schizophrenia	Schizophrenia resistant to the typical agents
Main adverse effects	More extrapyramidal Symptoms (EPS)	Less (EPS) High diabetes, hypercholesterolemia, and weight gain

Main differences between typical and atypical antipsychotic drugs

