Department of Anesthesia Technology

Pharmacology

2021-2022

Lecturer

Faris E. Mohammed

Lecture 6

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. **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, 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** Procaine Chloroprocaine Tetracaine Cocaine	**Amides** Lidocaine, Bupivacaine Ropivacaine, Mepivacain 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

Department of Anesthesia Technology

Pharmacology (theory)

2021-2022

Lecturer

Faris E. Mohammed **Lecture 6**

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.

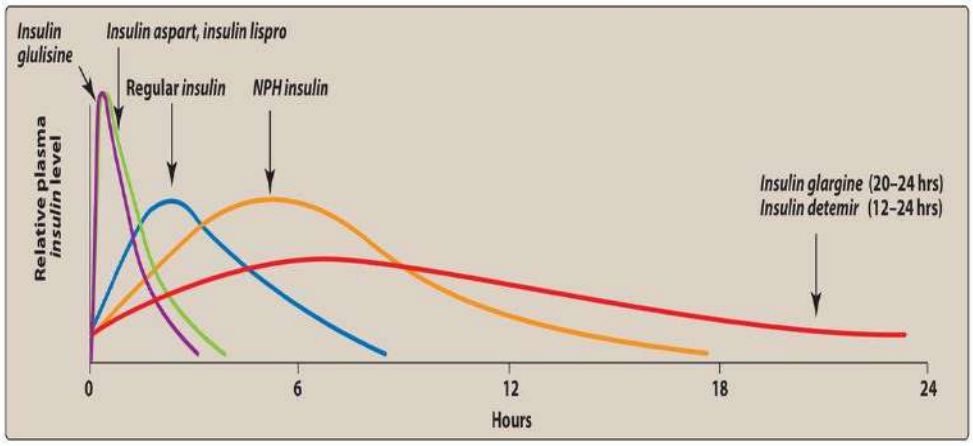
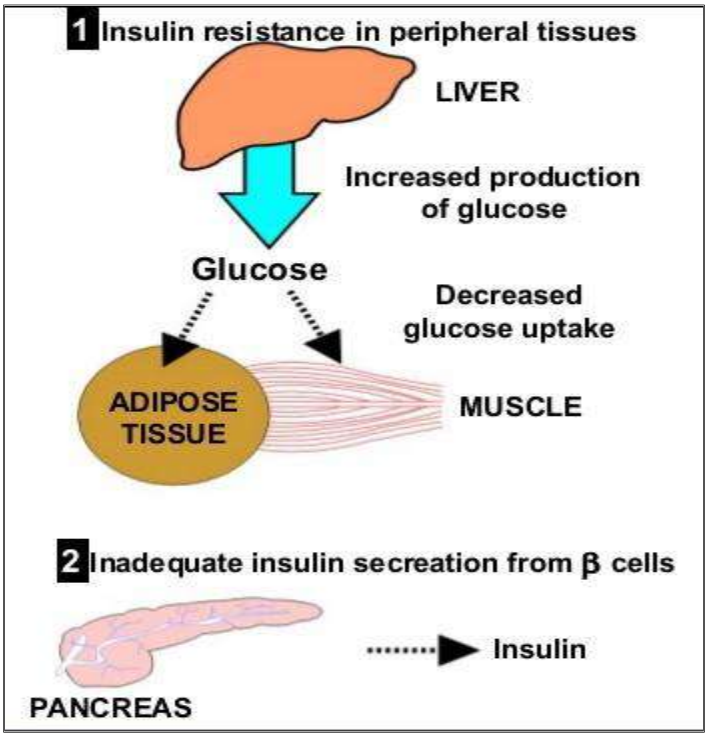


Figure 24.7
Onset and duration of action of human *insulin* and insulin analogs. NPH = neutral protamine Hagedorn.

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 hypoglycemic drugs

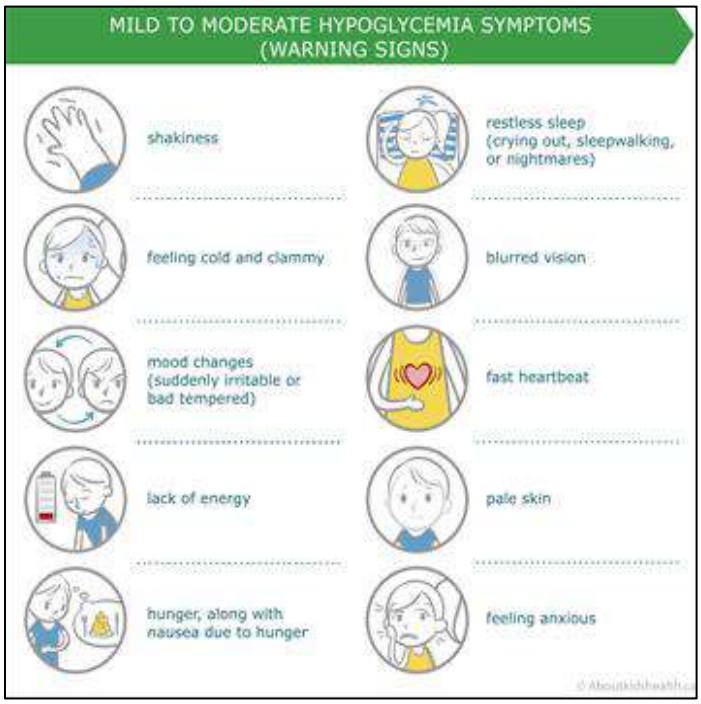
Sulfonylureas (glibenclamide) these agents are classified as insulin secretagogues, because they promote insulin release from the β cells of the pancreas.

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, Ca2+ 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



Biguanides (Metformin)

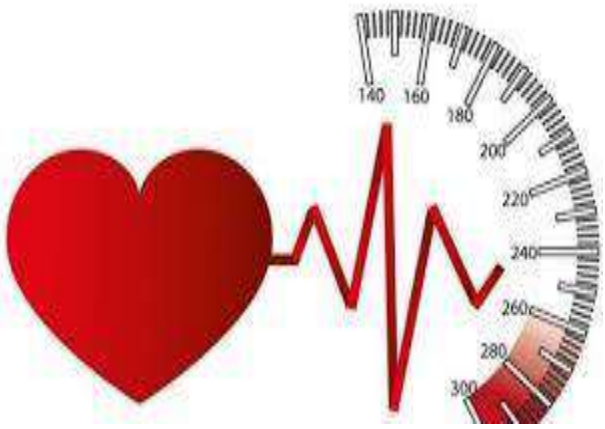
The main mechanism of action of metformin is reduction of hepatic gluconeogenesis. [Note: Excess glucose produced by the liver is a major source of high blood glucose in type 2 diabetes, accounting for high fasting blood glucose.] Metformin also slows intestinal absorption of sugars and improves peripheral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



Drug acting on the lower digestive system

Anesthetic Department

Pharmacology (theory)

Lec 8

LECTURER

FARIS E. MOHAMMED

Anti-diarrheal

- Increased motility of the GI tract and decreased absorption of fluid are major factors in diarrhea. Antidiarrheal drugs include anti motility agents, adsorbents, and drugs that modify fluid and electrolyte transport

Anti-diarrheal

A- Anti-motility agents

Two drugs that are widely used to control diarrhea are diphenoxylate and loperamide Both are analogs of meperidine and have opioid-like actions on the gut. They activate presynaptic opioid receptors in the enteric nervous system to inhibit acetylcholine release and decrease peristalsis. At the usual doses, they lack analgesic effects

Anti-diarrheal

B- Adsorbent agents

Such as aluminum hydroxide and methylcellulose are used to control diarrhea. Presumably, these agents act by adsorbing intestinal toxins or microorganisms and/or by coating or protecting the intestinal mucosa. They are much less effective than ant motility agents, and they can interfere with the absorption of other drugs.

Anti-diarrheal

C- Agents that modify fluid and electrolyte transport

Bismuth subsalicylate, used for traveler's diarrhea, decreases fluid secretion in the bowel. Its action may be due to its salicylate component as well as its coating action. Adverse effects may include black tongue and black stools.

Medication for constipation

LAXATIVE

Laxatives are commonly used for constipation to accelerate the movement of food through the GI tract.

LAXATIVE

A- Irritants and stimulants

1. Senna: This agent is a widely used stimulant laxative. Its active ingredient is a group of sennosides, a natural complex of anthraquinone glycosides. Taken orally, senna causes evacuation of the bowels within 8 to 10 hours. It also causes water and electrolyte secretion into the bowel.

2. Bisacodyl: Available as suppositories and enteric-coated tablets, bisacodyl is a potent stimulant of the colon. It acts directly on nerve fibers in the mucosa of the colon.

LAXATIVE

3. Castor oil

This agent is broken down in the small intestine to ricinoleic acid, which is very irritating to the stomach and promptly increases peristalsis. Pregnant patients should avoid castor oil because it may stimulate uterine contractions.

LAXATIVE

B- Bulk laxatives

The bulk laxatives include hydrophilic colloids (from indigestible parts of fruits and vegetables). They form gels in the large intestine, causing water retention and intestinal distension, thereby increasing peristaltic activity. Similar actions are produced by methylcellulose, psyllium seeds, and bran. They should be used cautiously in patients who are immobile because of their potential for causing intestinal obstruction.

LAXATIVE

C. Saline and osmotic laxatives

Saline cathartics, such as magnesium citrate and magnesium hydroxide, are nonabsorbable salts (anions and cations) that hold water in the intestine by osmosis. This distends the bowel, increasing intestinal activity and producing defecation in a few hours.

LAXATIVE

D. Stool softeners (emollient laxatives or surfactants)

Surface-active agents that become emulsified with the stool produce softer feces and ease passage. These include docusate sodium and docusate calcium. They may take days to become effective and are often used for prophylaxis rather than acute treatment. Stool softeners should not be taken concomitantly with mineral oil because of the potential for absorption of the mineral oil.

LAXATIVE

E. Lubricant laxatives

Mineral oil and glycerin suppositories are lubricants and act by facilitating the passage of hard stools. Mineral oil should be taken orally in an upright position to avoid its aspiration and potential for lipid or lipoid pneumonia


THANKS
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Department of Anesthesia Technology

Pharmacology

(Theory)

2021-2022

Lecturer

Faris E. Mohammed **Lecture ( )**

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:

Benzodiazepines should be used cautiously in patients with liver disease.

Drowsiness and confusion.

Ataxia.

Cognitive impairment.

Tolerance.

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-HT1A) 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:

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

Department of Anesthesia

Pharmacology (theory)

2021-2022

Lecturer

Faris E. Mohammed

Lecture (10)

Hyperlipidemia

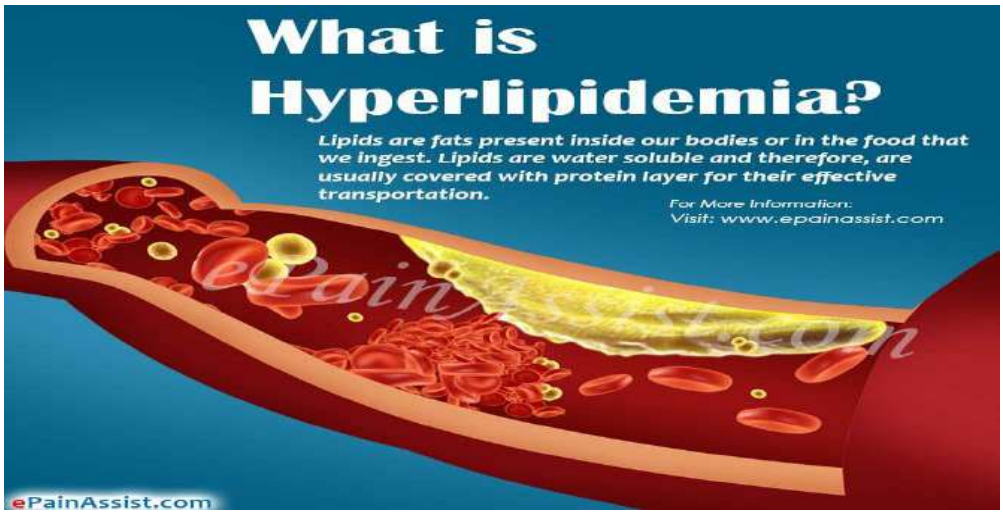
Plasma lipids consist mostly of lipoproteins, which are spherical complexes of lipids and specific proteins (apolipoproteins).

The clinically important lipoproteins, listed in decreasing order of atherogenicity, are LDL, very–lowdensity lipoprotein (VLDL) and chylomicrons, and HDL.

Cholesterol levels may be elevated due to lifestyle factors (for example, lack of exercise or diet containing excess saturated fats). Hyperlipidemias can also result from an inherited defect in lipoprotein metabolism or, more commonly, from a combination of genetic and lifestyle factors

The occurrence of CHD is positively associated with high total cholesterol and more strongly with elevated LDL-C. [Note: Total cholesterol is the sum of LDL-C, VLDL-C, and HDL-C.] In contrast to LDL-C, high levels of HDL-C have been associated with a decreased risk for heart disease

Reduction of LDL-C is the primary goal of cholesterol- lowering therapy.



Treatment options for hypercholesterolemia:

Lifestyle changes, such as diet, exercise, and weight reduction, can lead to modest decreases in LDL-C and increases in HDL-C. However, most patients are unable to achieve significant LDL-C reductions with lifestyle modifications alone, and drug therapy may be required.

Elevated triglycerides are independently associated with increased risk of CHD. Diet and exercise are the primary modes of treating hypertriglyceridemia. If indicated, niacin and fibric acid derivatives are the most efficacious in lowering triglycerides. Omega-3 fatty acids (fish oil) in adequate doses may also be beneficial. Triglyceride reduction is a secondary benefit of the statins, with the primary benefit being reduction of LDL-C.

DRUGS FOR HYPERLIPIDEMIA:

A. HMG CoA reductase inhibitors: (Lovastatin simvastatin, pravastatin, atorvastatin, fluvastatin, pitavastatin, and rosuvastatin)

3-Hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitors (commonly known as statins) lower elevated LDL-C, resulting in a substantial reduction in coronary events and death from CHD.

Therapeutic benefits:

Include plaque stabilization, improvement of coronary endothelial function, inhibition of platelet thrombus formation, and anti-inflammatory activity.

they deplete the intracellular supply of cholesterol, depletion of intracellular cholesterol causes the cell to increase the number of cell surface LDL receptors that can bind and internalize circulating LDLs. Thus, plasma cholesterol is reduced.

Adverse effects:

Elevated liver enzymes may occur with statin therapy. Therefore, liver function Myopathy and rhabdomyolysis (disintegration of skeletal muscle; rare) have been reported

B. Niacin (nicotinic acid) Niacin can reduce LDL-C by 10% to 20% and is the most effective agent for increasing HDL-C. It also lowers triglycerides by 20% to 35%.

Mechanism of action: At gram doses, niacin strongly inhibits lipolysis in adipose tissue, thereby reducing production of free fatty acids. The liver normally uses circulating free fatty acids as a major precursor for triglyceride synthesis. Reduced liver triglyceride levels decrease hepatic VLDL production, which in turn reduces LDL-C plasma concentrations.

Adverse effects: The most common side effects of niacin are an intense cutaneous flush (accompanied by an uncomfortable feeling of warmth) and pruritus.

C. Fibrates:

Fenofibrate and gemfibrozil are derivatives of fibric acid that lower serum triglycerides and increase HDL levels.

Adverse effects: The most common adverse effects are mild gastrointestinal (GI) disturbances.

D. Bile acid–binding resins

Bile acid sequestrants (resins) have significant LDL cholesterol– lowering effects, although the benefits are less than those observed with statins.

Mechanism of action:

Cholestyramine colestipol anion-exchange resins that bind negatively charged bile acids and bile salts in the small intestine The resin/bile acid complex is excreted in the feces, thus lowering the bile acid concentration. This causes hepatocytes to increase conversion of cholesterol to bile acids, which are essential components of the bile. Consequently,

intracellular cholesterol concentrations decrease, which activates an increased hepatic uptake of cholesterol- containing LDL particles, leading to a fall in plasma LDL-C.

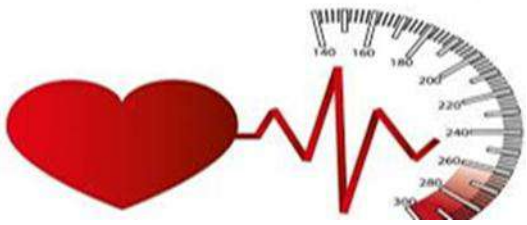
Adverse effects:

GI disturbances, such as constipation, nausea, and flatulence.

E. Omega-3 fatty acids:

Omega-3 polyunsaturated fatty acids (PUFAs) are essential fatty acids that are predominately used for triglyceride lowering. Essential fatty acids inhibit VLDL and triglyceride synthesis in the liver. The omega-3 eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)

The most common side effects of omega-3 include GI effects (abdominal pain, nausea, diarrhea) and a fishy aftertaste.



Department of Anesthesia

Pharmacology

Practical

2021-2022

Lecturer

Faris E. Mohammed **Lec (6)**

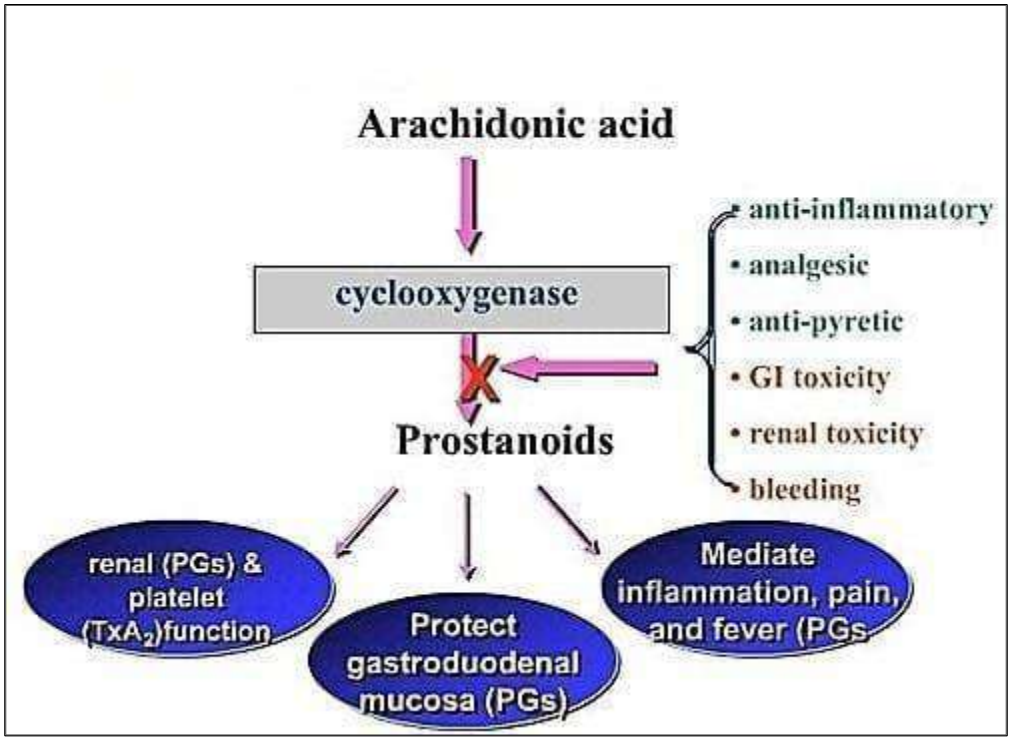
Non-narcotic analgesics

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.

Mechanism of action:

They act primarily by inhibiting the cyclooxygenase enzymes (COX_1) 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.

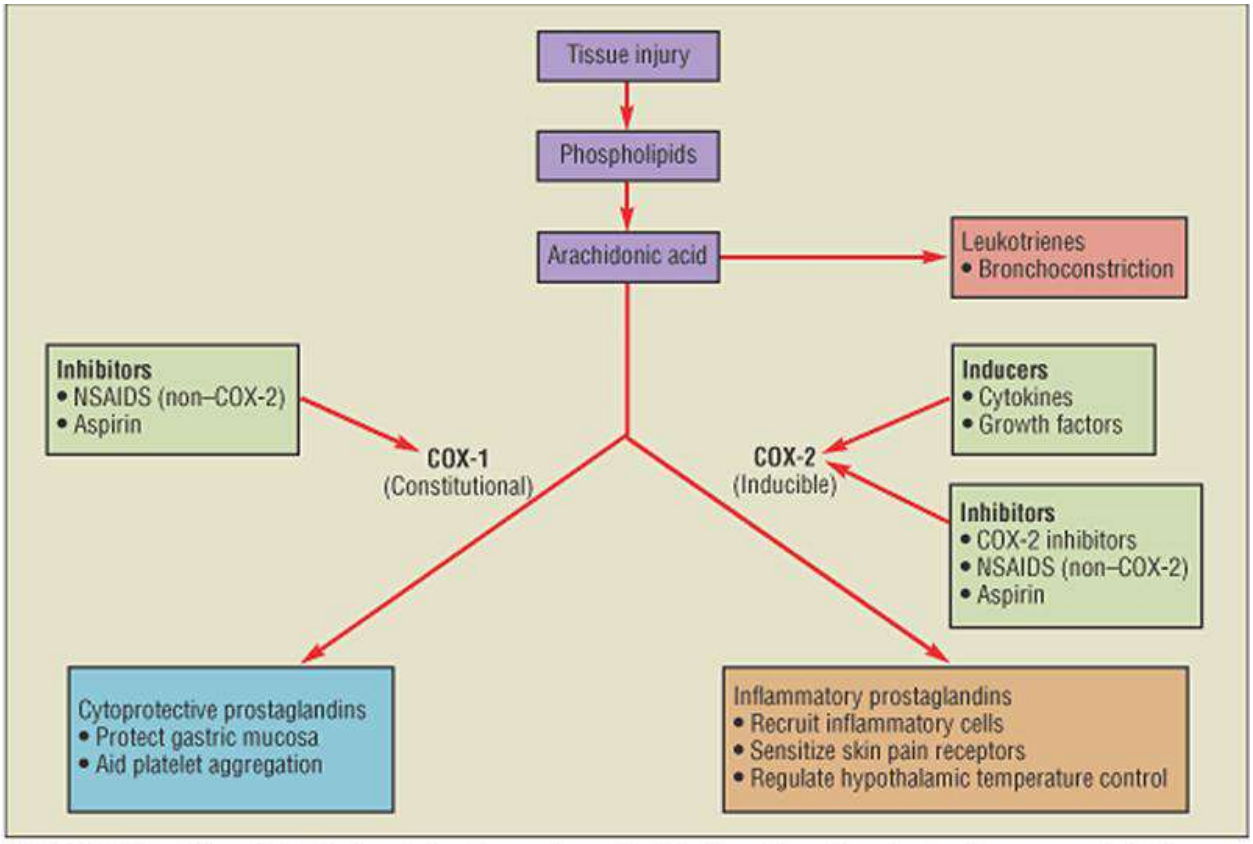


FIGURE 1. Algorithm of the biochemical pathway shows that the formation of prostaglandins occurs via both cyclooxygenase enzymes (COX-1 and COX-2).

1. Aspirin

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

2. Acetaminophen

- Headache: inhibit cyclooxygenase (COX_3) in the brain
- Anti-pyretic.

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

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

Contraindicated:

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

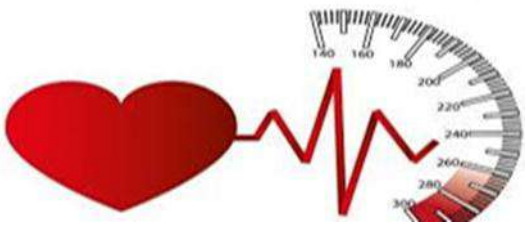
Adverse effects:

Increase blood pressure, Gastric erosion, gastric bleeding, and bronchospasm.

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



Department of Anesthesia

Pharmacology

Practical

2021-2022

Lecturer

Faris E. Mohammed

Lecture (9)

Narcotic analgesics

Opioid analgesics

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.

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).

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.

4. Depression of cough reflex: Both morphine and codeine have antitussive properties.

5. Miosis: The pinpoint 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.

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.

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. 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 Anesthesia Technology

Pharmacology

(Theory)

2021-2022

Lecturer

Faris E. Mohammed **Lecture ( )**

Anxiolytics and Sedative

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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:

Benzodiazepines should be used cautiously in patients with liver disease.

Drowsiness and confusion.

Ataxia.

Cognitive impairment.

Tolerance.

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-HT1A) 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:

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

الأدوية عملي

محاظرة 1

Introduction, Definition in Pharmacology
Pharmacology Lab 1

Lecturer

Faris E. Mohammed

Pharmacology

Pharmacology is the study of the action and effects of drugs on living systems and the interaction of drugs with it.

It’s the Study of biochemical, physiological and pathological changes caused by drugs in the body.

Drug: a chemical substance that act and alters biologic activity in a person, or pathological states for the benefits of the patients.

Source of Drugs

1. Natural

- Plants
- Animals
- Microorganisms
- Mineral

2. Synthetics

- Semisynthetic
- Synthetic

Source of Drugs

- **Plant source**

Digoxin from digitalis plant.

Quinine obtained from cinchona plant.

Morphine from opium.

- **Animal source**

Insulin from Pork pancreas

Vitamin B 12 from liver extract

Pepsin from stomach of cow.

Cod liver oil from cod fish liver.

Source of Drugs

Microorganism Sources

Bacteria, Fungi, Moulds are important sources of many life saving drugs.

Examples:

Penicillin obtained from penicillium notatum.

Chloramphenicol from Streptomyces venezuelace.

Streptomycin from Streptomyces griseus.

Neomycin from Streptomyces fradiae.

Source of Drugs

Mineral

- Ferrus sulfate anemia
- Magnesium sulfate purgative
- Sodium bicarbonate antacid
- Aluminum hydroxide antacid

Source of Drugs

Synthetic drugs:

Presently majority of drugs are obtained synthetically . Prepared by chemical synthesis in pharmaceutical laboratories.

Diphenoxylate , aspirin, oral antidiabetics, antihistamines , paracetamol.

Semisynthetic drugs:

Prepared by chemical modification of natural drugs.

Penicillins from 6 amino penicillanic acid which obtained from the mould penicillium notatum.

Source of Drugs

Human source

Menotrophins from post menopausal women urine.

Human insulin was manufactured through recombinant DNA technology.

Pharmacology

Medical pharmacology:

The study of drugs used for the diagnosis, prevention, and treatment of disease.

Pharmacology

1.Pharmacodynamic

Processes describe the actions of the drug on the body, i.e what the drug does to the body, the effects of the drug on the body .

2. Pharmacokinetic

Processes describe the action of the body on the drug, i.e. what the body does to drugs, or study the fate of the drugs in the body.

Pharmacokinetic processes including absorption, distribution, metabolism, and excretion(elimination).

Pharmacology

Over the counter drugs (OTC)

Medicines sold directly to a consumer without a prescription from a healthcare professional (physician), as opposed to prescription drugs, which may be sold only to consumers possessing a valid prescription.

Pharmacology

Examples of OTC drugs:

Pain and fever relievers: like acetaminophen (paracetamol) and NSAIDS like ibuprofen, diclofenac, and naproxen.

Cough medicines such as dextromethorphan.

Antihistamines like Loratadine, Diphenhydramine.

Decongestsnt: like pseudoephedrine, phenylephrine (orally) and as nasal spray like Oxymetazoline and phenylephrine.

Drugs for diarrhea: like loperamide.

Pharmacology

The dose: is the amount of drug taken at any one time.

weight of drug (e.g. 250 mg)

volume of drug solution (e.g. 10 mL, 2 drops), the number of dosage forms (e.g. 1 capsule, 1 suppository) or some other quantity (e.g. 2 puffs, in case of inhaler).

The dosage regimen is the frequency at which the drug doses are given.

Examples include 2.5 mL twice a day, one tablet three times a day, one injection every four weeks, one capsule 3 times daily.

Pharmacology

The dosage form

the physical form of a dose of drug.

Common dosage forms include tablets, capsules, syrups, suspension, creams, ointments, ampoules , vials, aerosols and patches.

The strength is the amount of drug in the dosage form or a unit of the dosage form.

Examples: 500 mg capsule, 250 mg/5 mL suspension, 160 mg tablets, (o.1 mg/ dose , puff , inhaler), 5mg/ 1ml eye drops, 25mg/ ml ampoule, 600mg/ 5ml ampoule.

Pharmacology

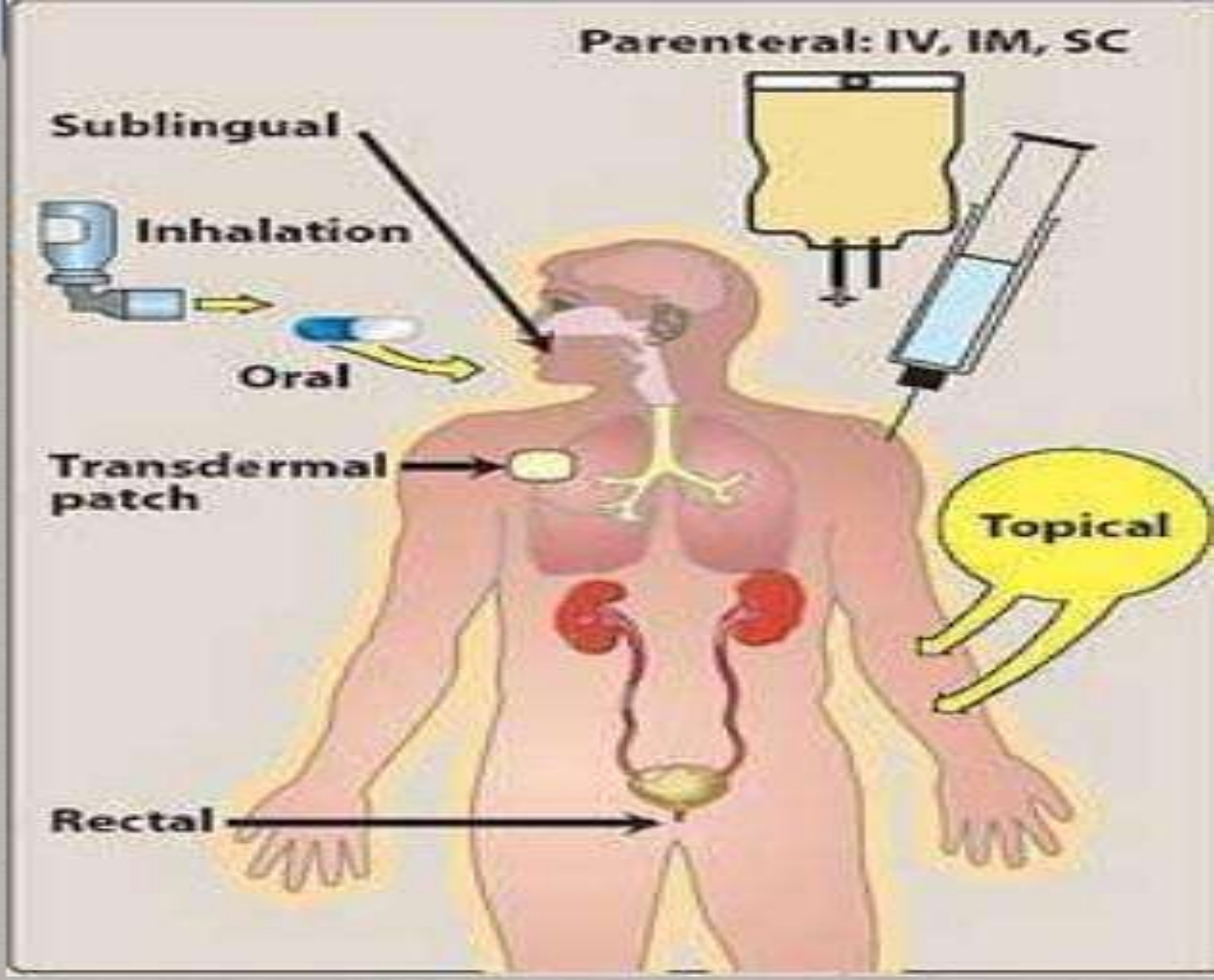
The route of administration:

is the way the dosage form is given. Common routes of administration, include oral, rectal, vaginal, inhalation , sublingual, nasal, otic , ocular, IV,IM, SC and topical.

Pharmacology

ROUT OF ADMENSTRATION

- Oral
- Parenteral I.V. I.M.
- Topical
- Inhaled
- Ophthalmic
- Otic
- Rectal
- Vaginal


Parenteral: IV, IM, SC
Sublingual
Inhalation
Oral
Transdermal patch
Topical
Rectal

Type of dosage form

1. Solid

- Tablets (conventional, chewable, sublingual, extended release).
- Capsules (hard and soft gelatin).
- Powder.
- Suppository.

Type of dosage form

2. Liquid (solution, suspension, emulsion).

3. Semisolid (ointment, cream, paste).

4. Gases (aerosol).


BAYER ASPIRIN
Bayer
for relief of headache pain and fever
alamy stock photo


Ventolin
Evohaler
200


FIRST AID ANTIBIOTIC
Triple Antibiotic Ointment

Drug nomenclature

Nonproprietary (generic) names

A term referring to the chemical makeup of a drug rather than to the advertised brand name under which the drug is sold.

Examples:

Propranolol,

Atorvastatin,

Clopidogrel,

Valsartan .

Drug nomenclature

Trade names

For drugs that make it all the way through development, testing, and regulatory acceptance, the pharmaceutical company then gives the drug a trade name, which is a standard term in the pharmaceutical industry for a brand

name or trademark name.

Examples:

Inderal, Indicardin (propranolol).

Vastor, Avas, Ateroz (Atorvastatin).

Antiplex, plagerine, platil (clopidogrel).

Arbiten, diovan (valsartan).

الأدوية عملي

محاظرة 2

Drug Metabolism and Excretion

Department Of Anesthesia Technology

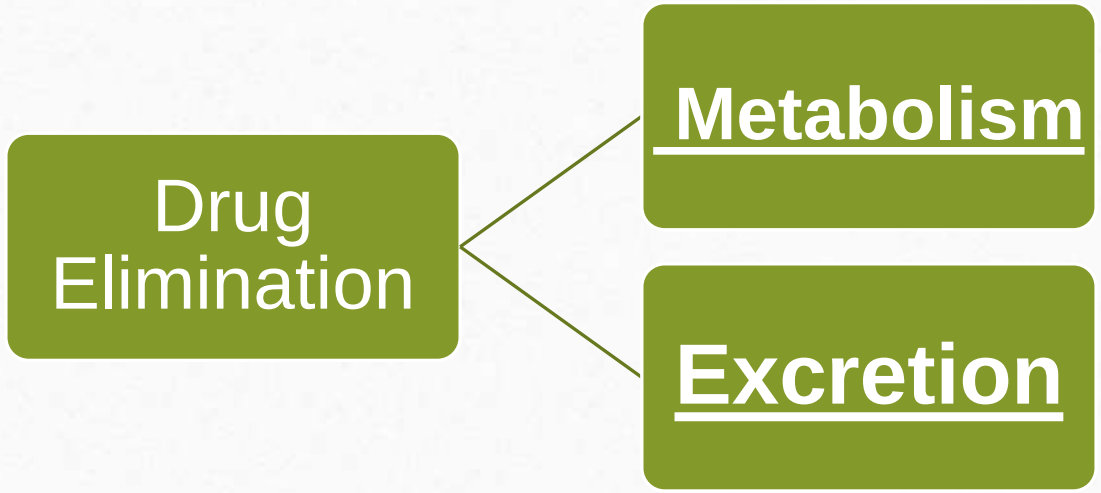
Practical pharmacology 2021-2022

2nd Stage

Lab 2: Faris E.Mohammed

Drug Elimination:

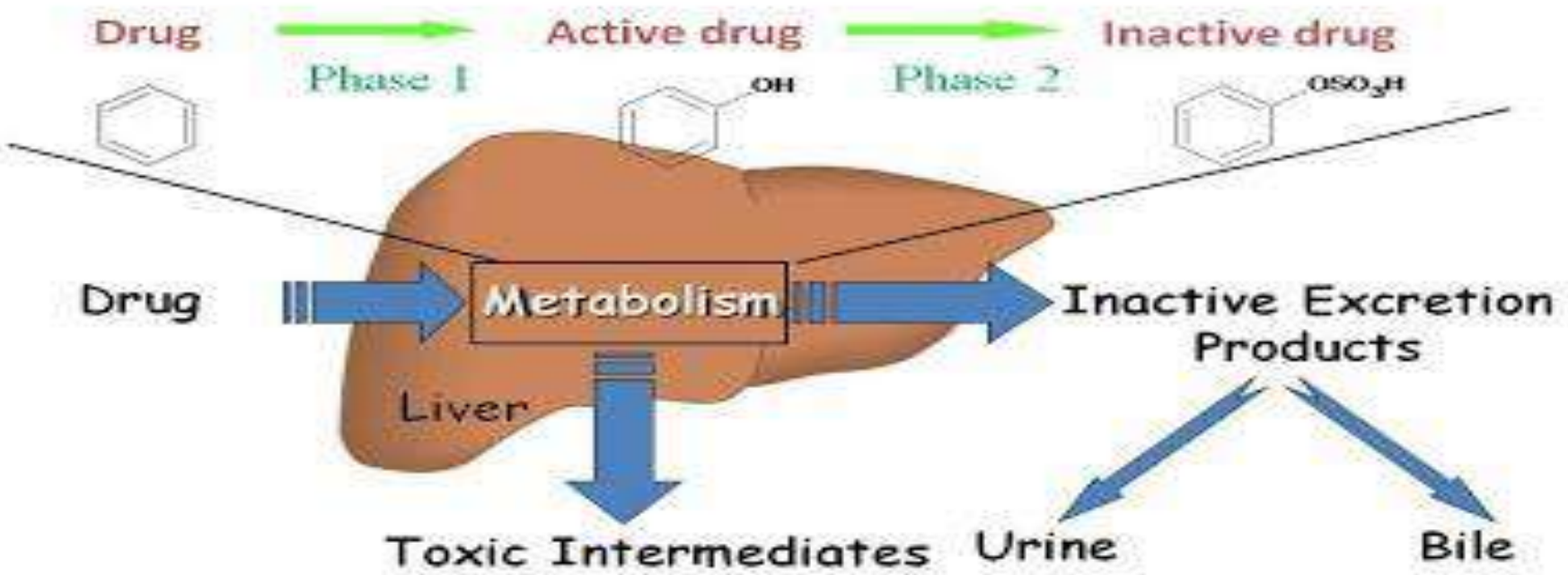
Drug elimination: is the irreversible loss of drug from the body. It occurs by two processes: metabolism and excretion.



BIOTRANSFORMATION
(Metabolism)

- Metabolism (Biotransformation): is the process by which the drug is chemically converted in the body to a metabolite. Biotransformation is usually an enzymatic process.
- The primary site for drug metabolism is liver.
- Non-polar **(lipid-soluble)** drugs → polar compounds **(water soluble)**
  - so they can excreted by the kidney or bile.

Drug Metabolism



Biotransformation of drugs may lead to the following:

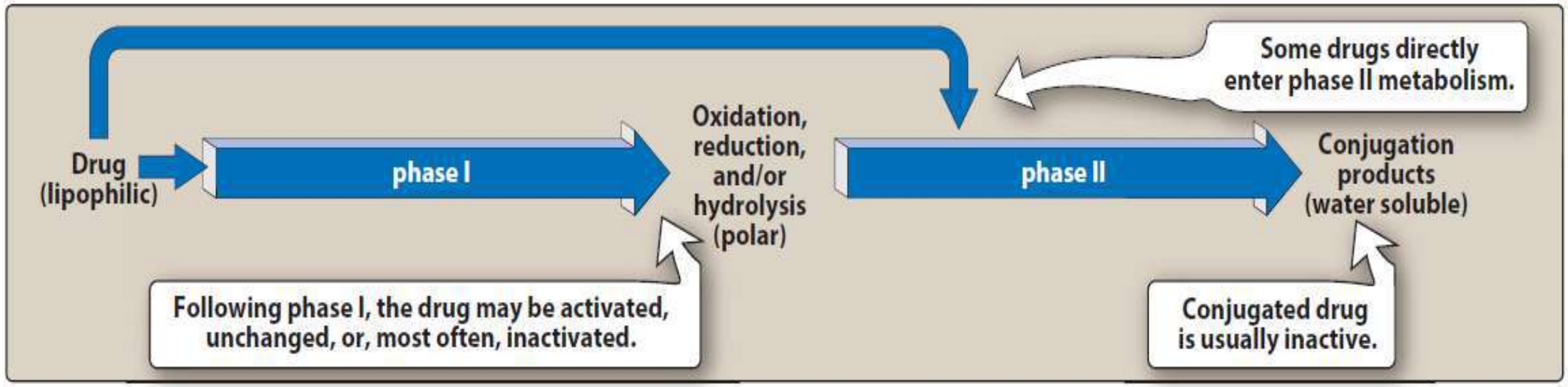
- Active Drug → In-active metabolite

such as metabolism of fentanyl to norfentanyl.

- Active Drug → Active Metabolite (Codiene to morphine)
- *Inactive Drug* → *Active (Prodrug)*

- **Prodrug:** is defined as a drug that has no pharmacologic activity before metabolism but that is converted by the liver to an active .
- The prodrug is stable, having better bioavailability or less side effects and less toxicity.
- **Example of prodrug :** Enalapril (metabolized to enaloprilat)

The biotransformation of drugs.



Biotransformation reactions can be classified into:

1- Phase I: Phase I reactions convert lipophilic drugs into more polar molecules by introducing or unmasking a polar functional group, such as –OH or –NH2 .

- **Phase I reactions usually involve : Oxidation, Reduction or Hydrolysis.**
- Phase I metabolism may increase, decrease, or have no effect on pharmacologic activity.

Enzymes that catalyzed phase 1 reactions:

- **Cytochrome P450:** The P450 system is important for the metabolism of many endogenous compounds (such as steroids, lipids) and for the biotransformation of exogenous substances (xenobiotics).
- Cytochrome P450, designated as CYPs, are family of enzymes involved in drug metabolism, that are located in most cells, but primarily in the liver and GI tract.
- CYP3A4 the most important enzyme for metabolism of most drugs.

1) CYP Inducers:

- **Some drugs increase activity of CYP enzymes so enhance the metabolism of drugs and decrease its concentration in the blood .**
- example:
  Certain drugs (for example, phenobarbital, rifampin, and chronic alcohol) are capable of increasing the synthesis of one or more CYP isozymes.

2) CYP Inhibitors:

- Inhibition of CYP isozyme activity ⟶ decrease metabolism of drugs ⟶ increase blood concentration in blood ⟶ drug interactions that lead to serious adverse effect.
- <u>Example on drugs that inhibit CYP enzyme:</u>
- Alcohol (acute) , Omeprazole, Erythromycin
- grapefruit juice

Drug Interaction

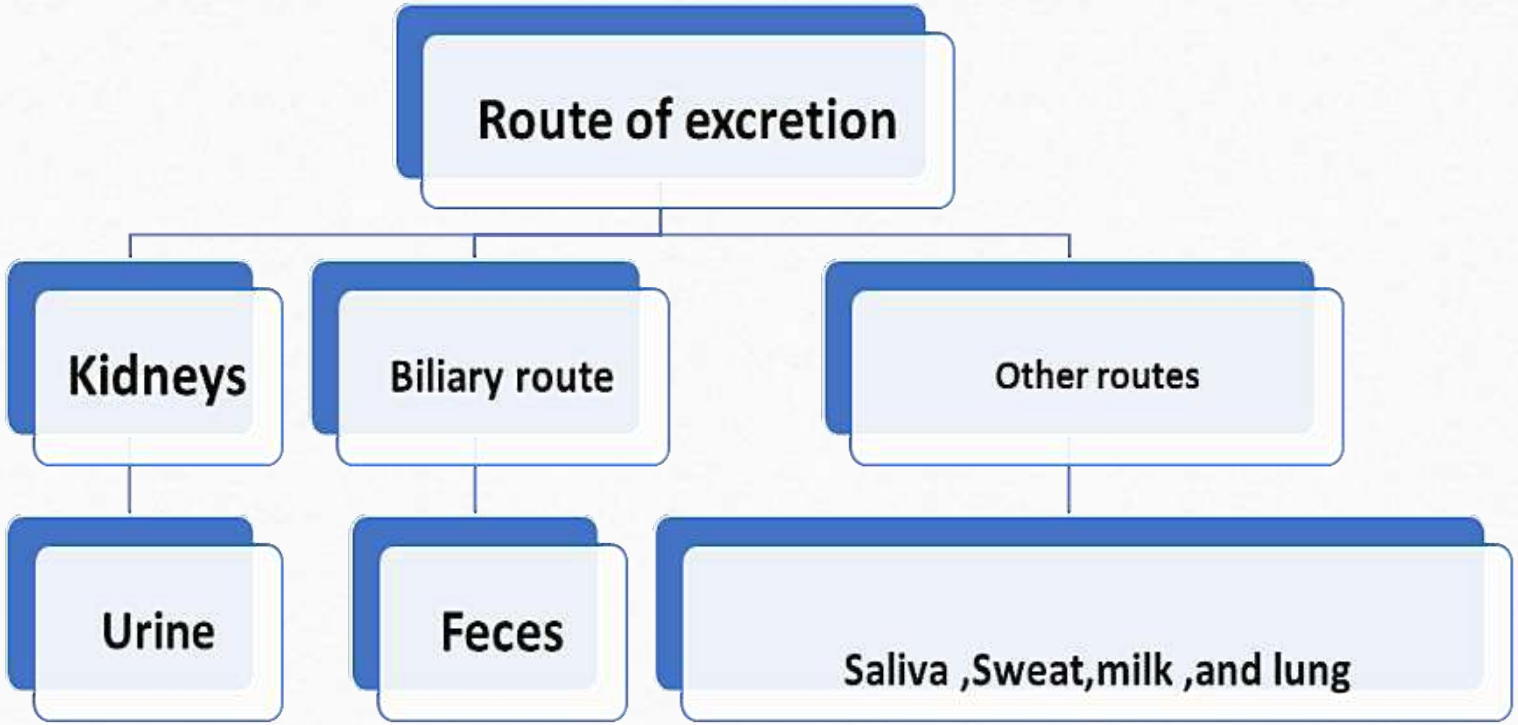
- Ex:
- **Warfarin and Omeprazole**
- omeprazole is a potent inhibitor the CYP isozymes responsible for warfarin metabolism. If the two drugs are taken together, plasma concentrations of warfarin increase, which leads to greater anticoagulant effect of warfarin and increased risk of bleeding.

Phase 2 metabolism:

- This phase consists of conjugation reactions. If the metabolite from phase I metabolism is sufficiently polar, it can be excreted by the kidneys or bile.
- many phase I metabolites are still too lipophilic and can not excreted., phase 2 reactions produce a metabolite with improved water solubility and increased molecular weight, which serves to facilitate the elimination of the drug from the kidney or bile.

❑What is excretion ?

Excretion : is the removal of drugs and their metabolites from the body.

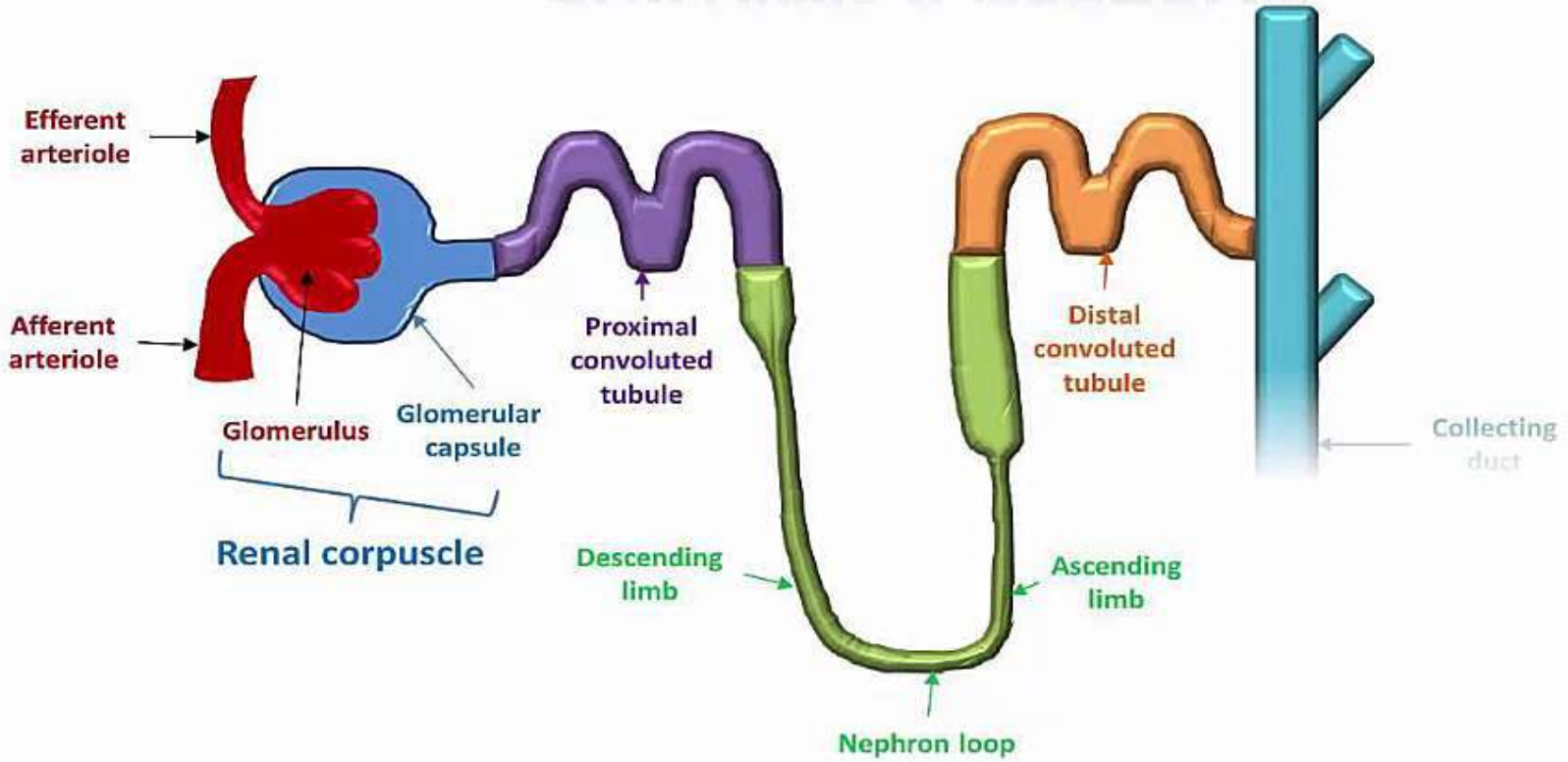


A. Renal Excretion

- The kidney is responsible for excreting all water-soluble substances and the molecular weight of the substances should be <500 Dalton
- **Renal excretion undergoes three stages :**

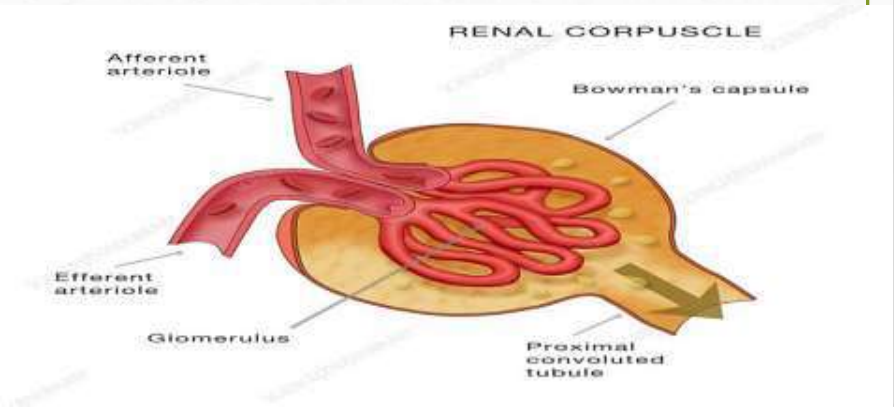
- **Glomerular filtration**
- **Tubular reabsorption**
- **Active Tubular secretion**

BUILDING A NEPHRON



1- Glomerular Filtration

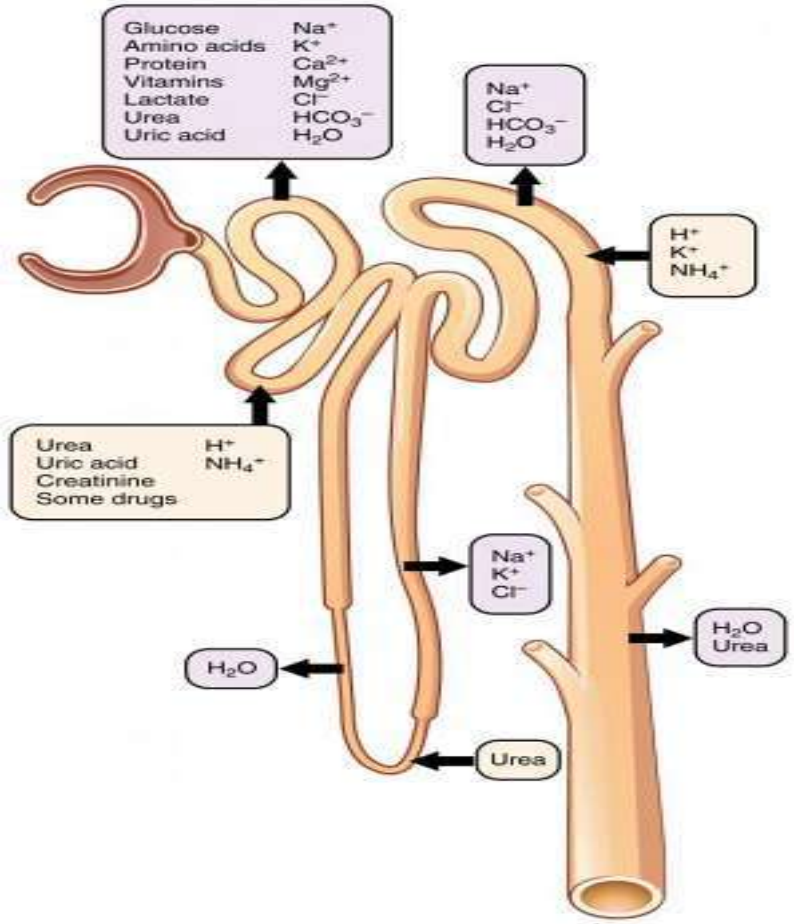
- Glomerular capillaries have pores with a unidirectional process that occurs for most small molecules (MW < 500 dalton), all **non protein binding drug** presented to the glomerulus is filtered. Thus, **glomerular filtration of a drug depends on its plasma protein binding and renal blood flow.**
-



2- **Tubular Reabsorption**

- Tubular reabsorption is a passive or active process whereby drugs are reabsorbed into the systemic circulation from the lumen of the distal tubules.
- Most of the reabsorption of solutes necessary for normal body function such as amino acids, glucose, and salts takes place in the proximal part of the tubule.

Tubular Reabsorption



3- Active Tubular Secretion

- Active renal secretion is a carrier mediated system that requires energy input, because the drug is transported against a concentration gradient [low to high concentration].
- This is the active transfer of organic acids and bases by two transport systems
- which operate in the proximal tubules
- (a) System for secretion of organic acids (anions) Operates for penicillin, uric acid.
- (b) System for secretion of organic base (cations) operates for thiazides, histamine.

B-Biliary Route

- Relatively larger molecules (MW > 500) are eliminated in the bile.
- Drugs that attain high concentrations in bile are erythromycin, ampicillin, rifampin, tetracycline, oral contraceptives.
- Certain drugs are excreted directly in colon, e.g. purgatives, heavy metals.

C- Other routes

- **Saliva and sweat:**
- These are of minor importance for drug excretion. Lithium, iodide, rifampin and heavy metals are present in these secretions.

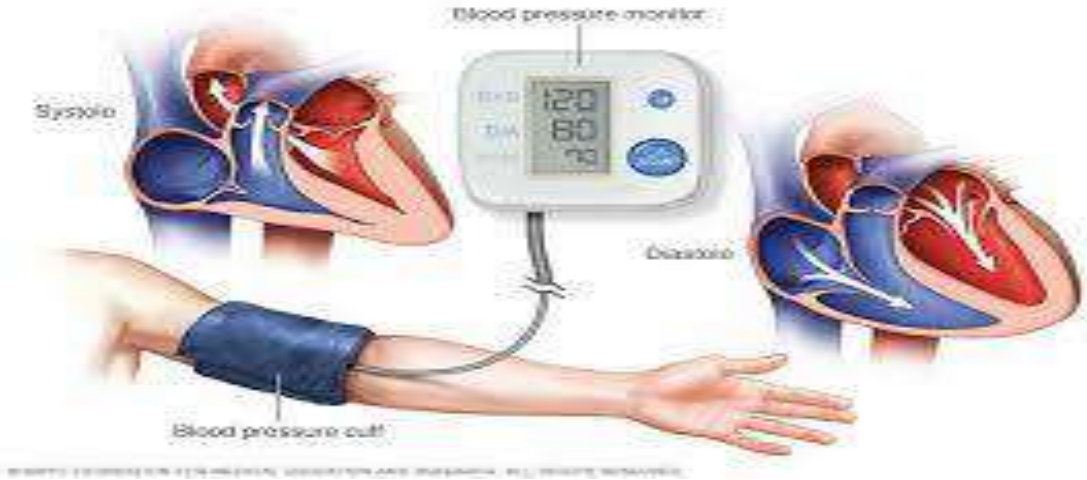
Exhaled air [lungs]:

Gases and volatile liquids (general anesthetics , alcohol) are eliminated by lungs, irrespective of their lipid solubility.


Thank You

الأدوية عملي

محاظرة 3



Effect of Some Drugs on Blood Pressure

Lecturer

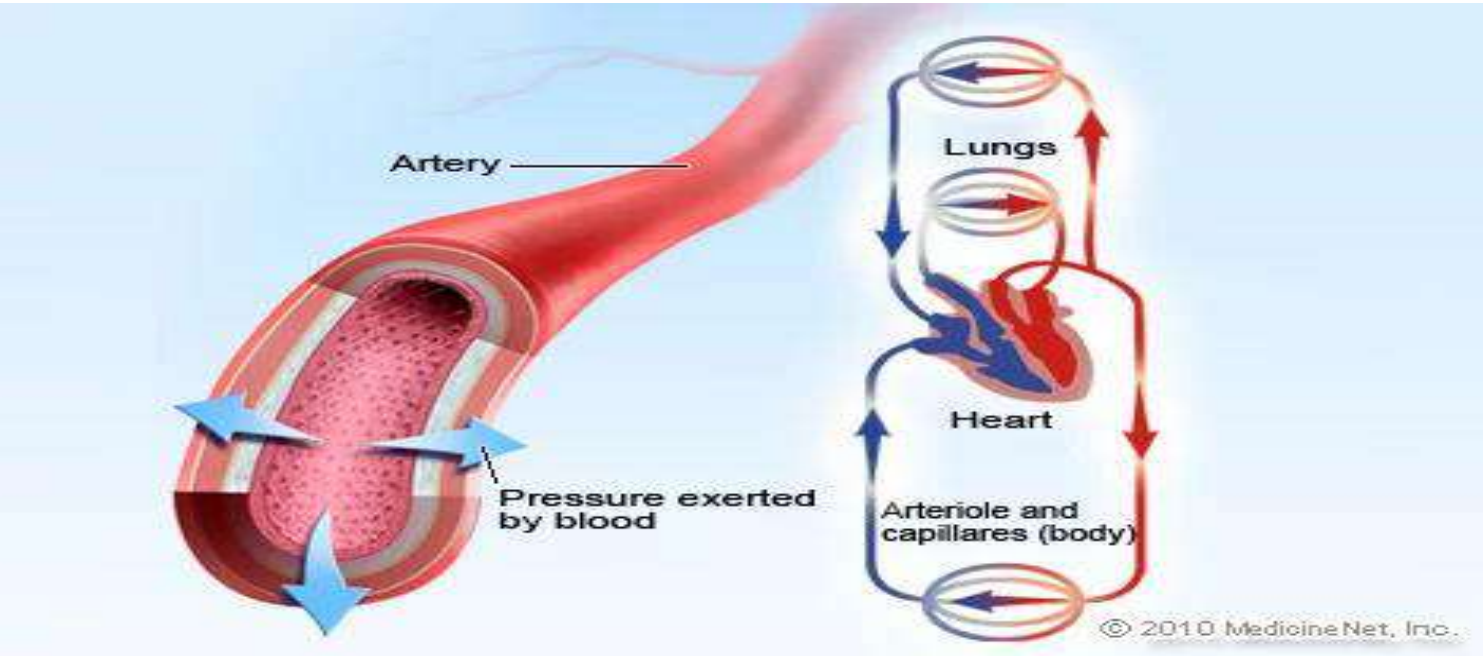
Dr. Faris E. Mohammed
Pharmacology

Lab 3

2021

Blood pressure (BP)

- Is the pressure exerted on the vessels that carry arterial (oxygenated) blood through out the body .
- It is divided into systolic (when the heart contracts) and diastolic (when the heart is filling) pressures.



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 may be:

➢ *primary* (essential hypertension—where the cause is not know.

➢ *secondary*—when it is secondary to other conditions like renal, endocrine or vascular disorders.

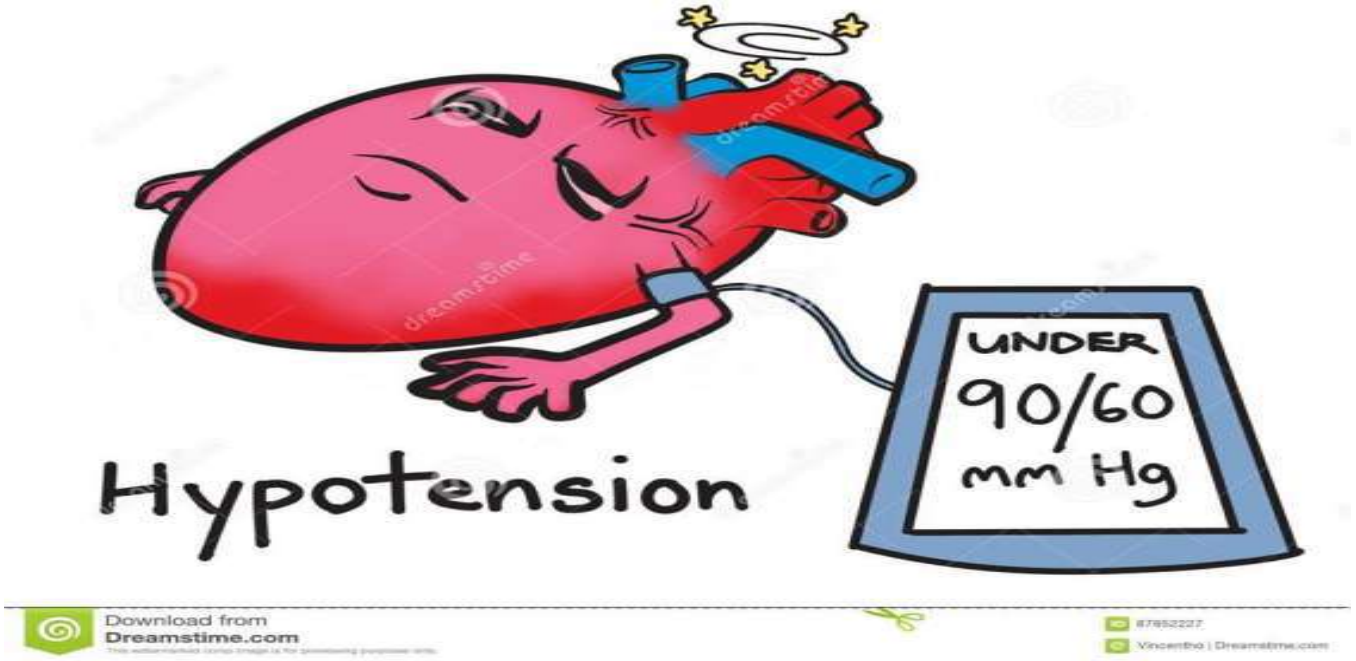
- (mm Hg) = millimeters of mercury

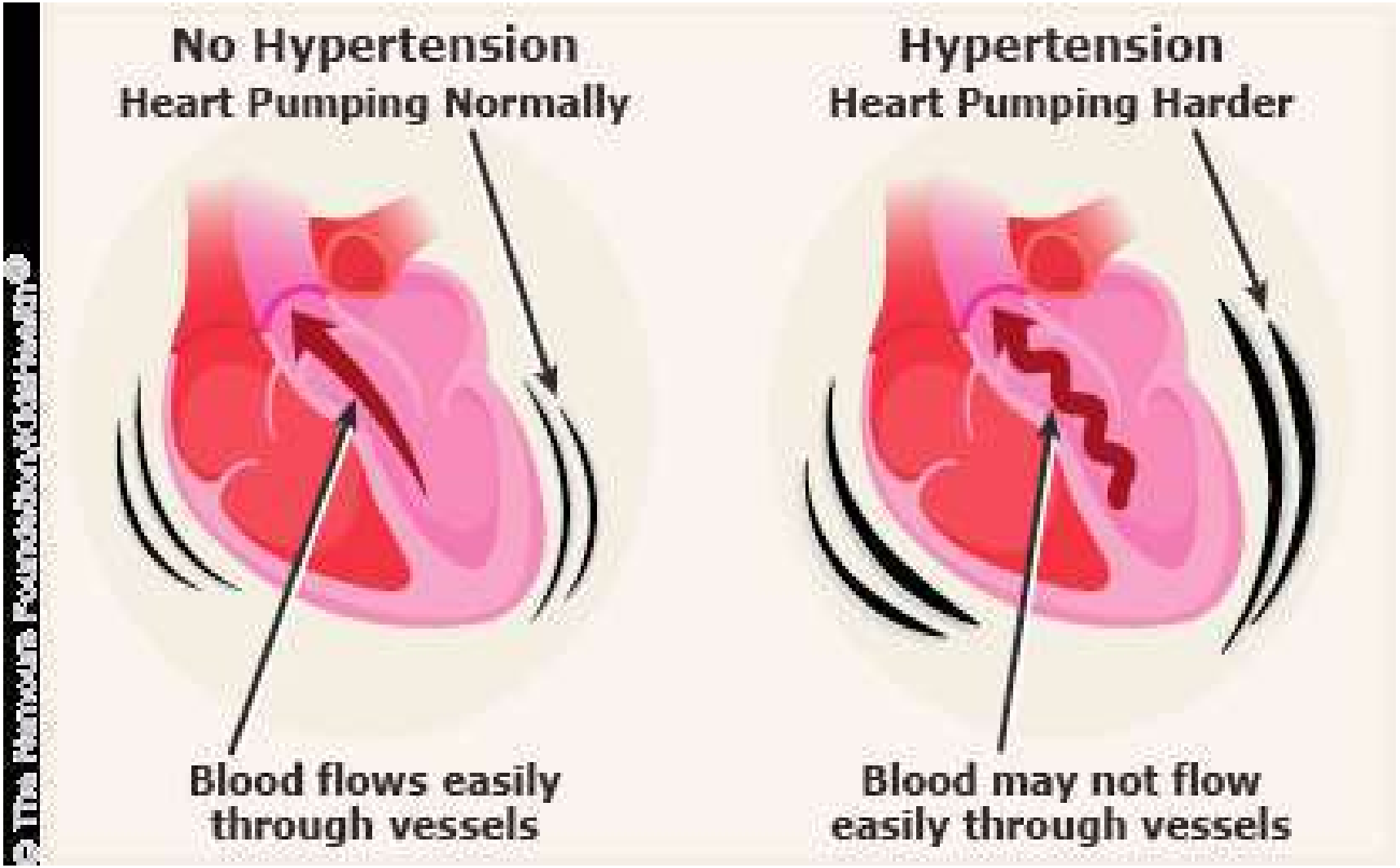
Hypotension

- Is the medical term for low blood pressure

(less than 90/60 mm Hg).

- The causes of low blood pressure can range from dehydration to serious medical or surgical disorders.




No Hypertension
Heart Pumping Normally
Blood flows easily through vessels
Hypertension
Heart Pumping Harder
Blood may not flow easily through vessels

Drugs induced hypertension

1- Non-Steroidal Anti-Inflammatory Drugs (NSAIDs):

Aspirin, Naproxen, Indomethacin, Ibuprofen ,

and Selective COX-2 inhibitor : Celecoxib

- NSAIDs prevent the synthesis of prostaglandins that are responsible for maintaining renal blood flow.
- Decreased synthesis of prostaglandins can result in retention of sodium and water and increase in blood pressure.
- Patients with a history of heart failure or kidney disease are at high risk.

2- corticosteroids

(e.g., hydrocortisone, dexamethasone, triamcinolone, betamethasone)

- The principal mechanism of corticosteroid- induced hypertension is the over stimulation of the mineralocorticoid receptor, resulting in sodium retention in the kidney. This results increase in blood pressure.
- The smallest effective dose and shortest duration of steroid therapy should be used in order to decrease the development of this adverse effect.
- Corticosteroid-induced hypertension may respond to diuretic therapy.

3- Sympathomimetic agent

- Sympathomimetic drugs that activate adrenergic receptors, they can raise **blood pressure** to alarming heights, particularly in hypertensive patients.

- Classification is based on mechanism of action

- Direct-acting agonists: e.g. epinephrine, norepinephrine.
- Indirect-acting agonists: e.g. amphetamine, Cocaine.
- Mixed-action agonists: e.g. Ephedrine, pseudo ephedrine, phenylpropanolamine and oxymetazoline (nasal decongestant).

Epinephrine (as a sympathomimetic drug)

Epinephrine added to local anesthetic solutions in low concentration, to increases the duration of local anesthesia by producing vasoconstriction at the site of injection.

Action of Epinephrine:

Epinephrine causes constriction in many networks of **blood** vessels .

In the heart, it increases the rate and force of contraction, Therefore, **epinephrine** may cause rapid raise in **blood pressure** (BP) and heart rate (HR).

4- Caffeine

- Caffeine is a central nervous system stimulant, used in combination with the analgesics e.g, acetaminophen and aspirin for the management of headaches in both prescription and over-the-counter products.
- A high dose of caffeine has positive inotropic and chronotropic effects on the heart, and increase blood pressure.

5- Oral contraceptives:

e.g (Estrogens and Progestins):

Chronic use of oral contraceptives may slightly **raise blood pressure** in certain women and may have other adverse effects on cardiovascular risk.

6- Dietary Supplements:

e.g Ginseng جينسينغ , Licorice عرق السوس

Mild stimulant effect , **Increase blood pressure.**

Generally, all patients with hypertension should discuss use of dietary supplements with their pharmacist or physician beforehand.

7- Immunosuppressant:

Immunosuppressant drugs are a class of drugs that suppress, or reduce, the strength of the body's immune system.

These drugs are given to patient who had an organ transplant, to make the body less reject a transplanted organ, such as a liver, heart, or kidney.

Some immunosuppressant can rise blood pressure, possibly because of the ways that can affect kidneys.

Examples of immunosuppressant that can increase blood pressure include:

- Cyclosporine
- Tacrolimus

Medications that can cause low blood pressure (Hypotension)

Many drugs can cause low blood pressure, including:

- **Diuretics** and other drugs that treat high blood pressure
- **Heart medications such as beta blockers.**
- **Drugs for Parkinson's disease**.
- Certain types of antidepressants **(tricyclic antidepressants)**
- Drugs for erectile dysfunction, **Sildenafil (Viagra),** particularly in combination with nitroglycerine; narcotics; and alcohol.


thank
YOU:-)

الأدوية عملي

محاظرة 4

Department of Anesthesia Technology

Pharmacology (Practical)

2021-2022

Lecturer

Faris E. Mohammed

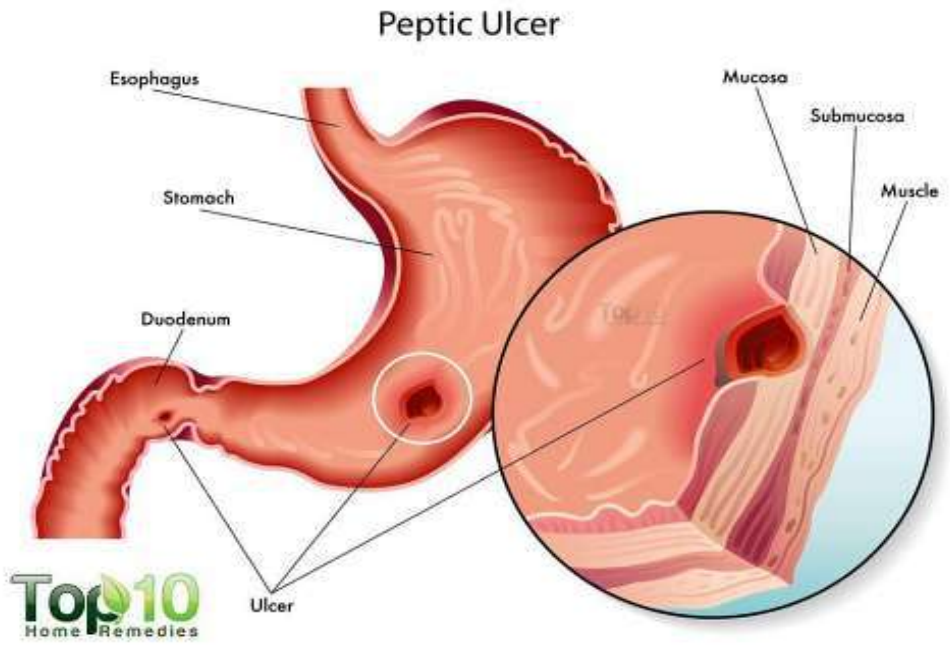
Lab 3

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).

Proton pump inhibitor PPIs:

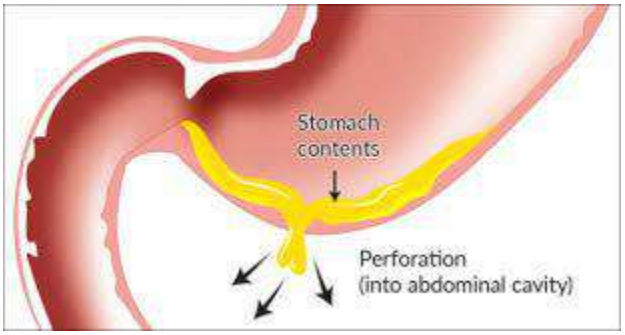
The PPIs bind to the H+/K+-ATPase enzyme system (proton pump) and suppress the secretion of hydrogen ions into the gastric lumen. The membrane-bound proton pump is the final step in the secretion of gastric acid. The available PPIs include esomeprazole, lansoprazole, omeprazole, pantoprazole, and rabeprazole.

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 (metronidazole may be used in penicillin-allergic patients) plus clarithromycin 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.

Mucosal protective agents

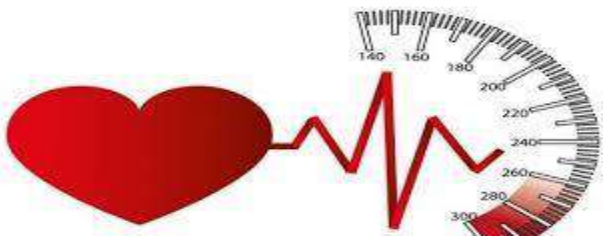
Also known as cytoprotective compounds, these agents have several actions that enhance mucosal protection mechanisms, thereby preventing mucosal injury, reducing inflammation, and healing existing ulcers.

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.

2. Bismuth subsalicylate:

Inhibits the activity of pepsin, increases secretion of mucus, and interacts with glycoproteins in necrotic mucosal tissue to coat and protect the ulcer.



الأدوية عملي

محاظرة 5

Antiemetics

DEPARTMENT OF ANESTHESIA TECHNOLOGY

PRACTICAL PHARMACOLOGY
2021-2022

2ND STAGE , LAB 4
LECTURER: FARIS E.MOHAMMED

Antiemetics: Drugs for Nausea and Vomiting

Nausea: is the feeling of the need to vomit. It includes an unpleasant sensation in the mouth and stomach and can be associated with salivation, sweating, dizziness, tachycardia.

Vomiting: is the forceful expulsion of the stomach contents through the mouth.

Causes of Nausea and Vomiting

•Drugs [chemotherapy, and Opioids].

•Motion sickness .

•Pregnancy.

•Migraine.

•The type of surgery: laparoscopic, middle ear.

• Duration of surgery

•Nonsmoker

•In previous decades anaesthesia was almost associated with vomiting ,but with the advent of new anaesthetic agents and more aggressive treatment the incidence of vomiting has decreased.

Physiology Of Nausea and Vomiting

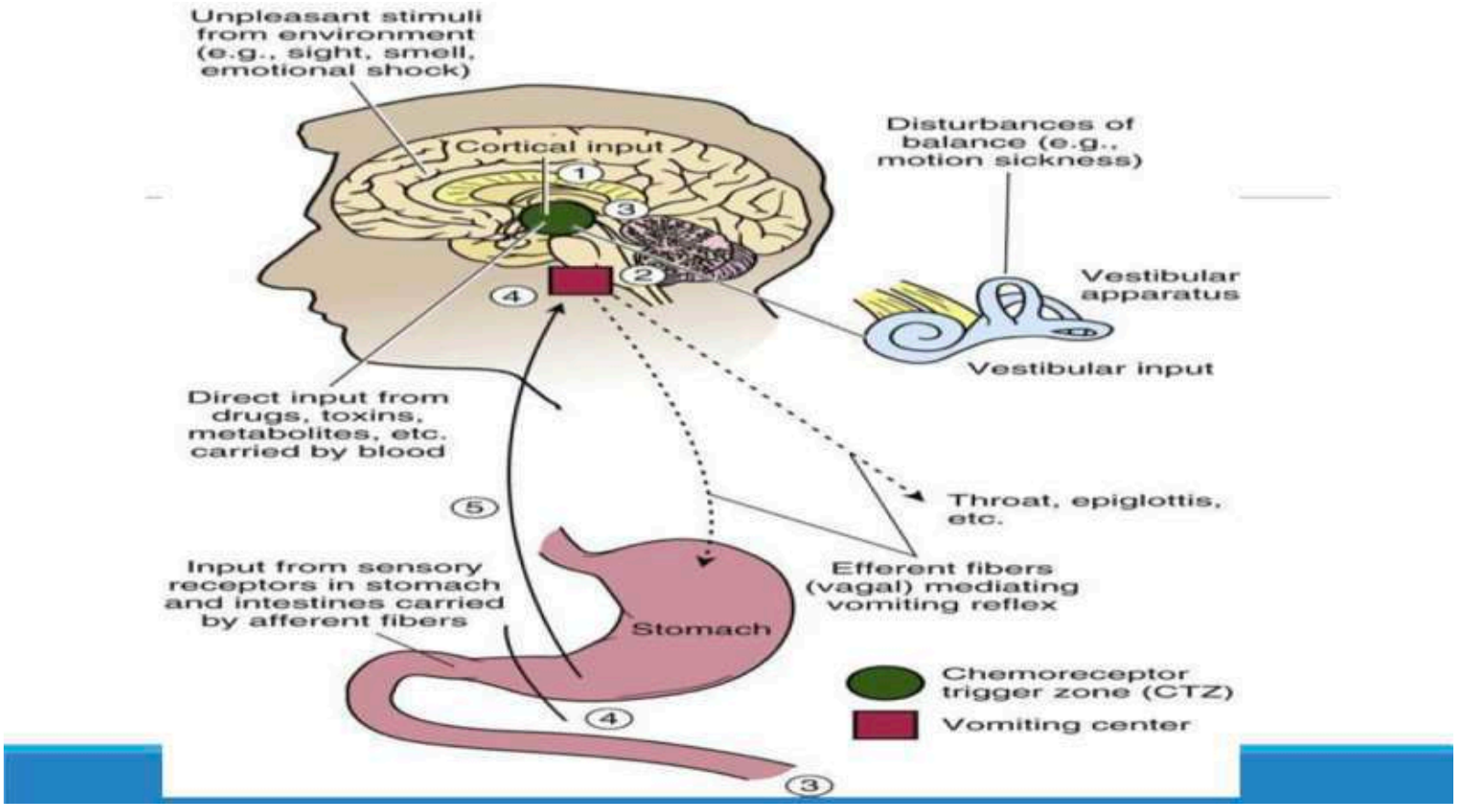
? The central nervous system[CNS], the peripheral nervous system ,and the gastrointestinal (GI) tract are all involved in initiating and coordinating the emetic response.

? In the CNS, the vomiting center(VC) receives incoming signals from other parts of the brain and the gastrointestinal [GI] tract and then coordinates the emetic response by sending signals to the effector organs.

? The VC is stimulated by neurotransmitters released from the chemoreceptor trigger zone(CTZ),the GI tract, the cerebral cortex, the , and the vestibular system

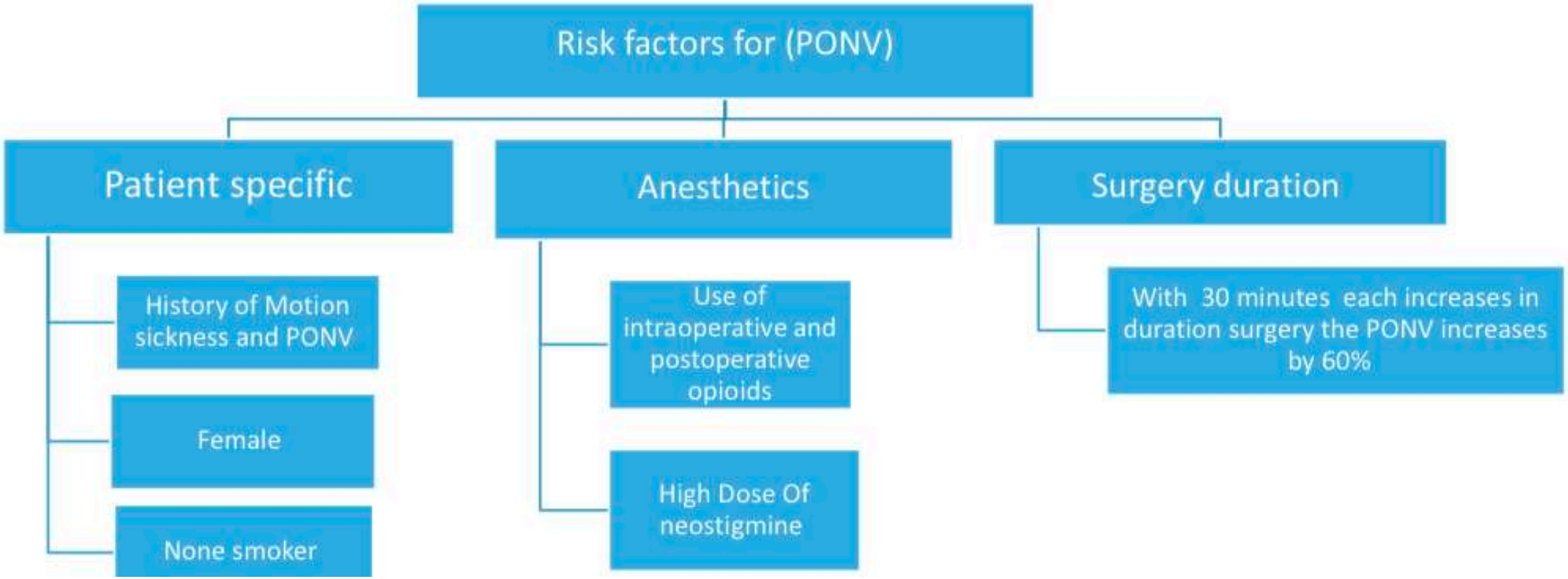
? The major neurotransmitter receptors associated with the emetic response include :

Serotonin(5-HT3)receptors , Dopamine receptors , Histamin , and acetylcholine receptors

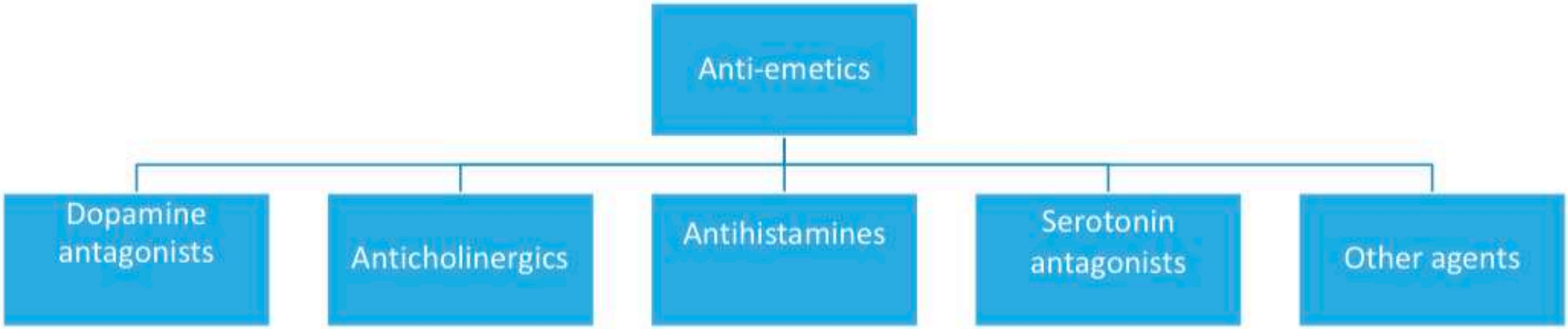


Post-Operative Nausea and Vomiting (PONV)

Postoperative nausea and vomiting[PONV], defined as nausea and/or vomiting occurring **within 24-48 hours after surgery**.



Anti-emetics classification:



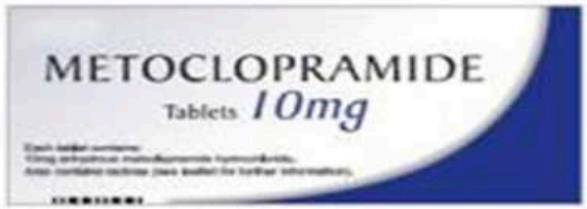
A- Dopamine antagonists:

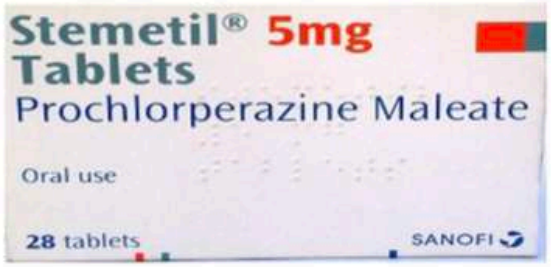
1- **Prochlorperazine**: is effective in the prevention and treatment of PONV.

2- **Domperidone**: Its used in children is limited to nausea and vomiting following chemotherapy or radiotherapy.

3**- Metoclopromide:** is given orally, and may be given intravenously (I.V)

Dopamine antagonist



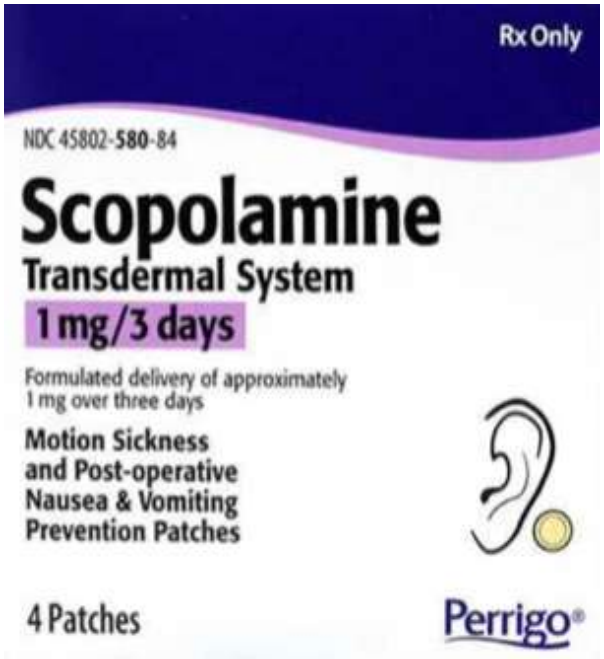


B- Anticholinergics:

While so-called‘ anticholinergic’ agents are effective antagonists at muscarinic receptors .

•Anticholinergic drugs: Hyoscine, Atropine

•Hyoscine [scopolamine]: Hyoscine has given with an intramuscular opioid as premedication, and in this will reduce PONV. It has also been used as a sedative and **amnesic agent (cause loss of memory).**



C- Antihistamine:

Antihistamine drugs: Cyclizine, Diphenhydramine, promethazine

Cyclizine : is used as an antiemetic in motion sickness, radiotherapy, PONV and emesis induced by opioids.

D- Serotonin antagonists

- **Ondansetron, Dolasetron, Tropisetron, and Granisetron.**

Ondansetron:

- uses: is indicated for the treatment of nausea and vomiting associated with chemo-or radiotherapy and in the peri-operative period.

Ondansetron is available as tablets (4–8 mg), a suppository (16 mg) and as a clear solution containing 2mg\ml for slow intravenous injection.

E- Other drugs

1-Dexamethasone: used as antiemetic for chemotherapy induced nausea and vomiting. And used at a dose of 2.5–10 mg to prevent post-operative nausea and vomiting. Its mode of action in this area is uncertain.

2- Benzodiazepines: (Lorazepam) is used as an antiemetic during chemotherapy. It has amnesic and sedative properties.

3-Combination regimens: Antiemetic drugs are often combined to increase antiemetic activity or decrease toxicity.

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محاظرة 1

Anesthetic Department

Pharmacology

2021-2022

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 Depending on their chemical properties, drugs may be absorbed from the GI tract by passive diffusion, facilitated diffusion, active transport, or endocytosis

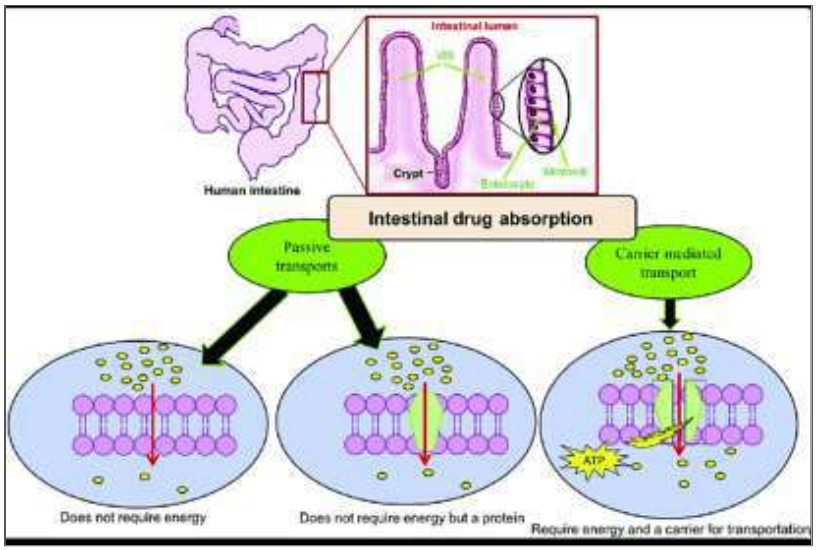
1. Passive diffusion: The driving force for passive absorption of a drug is the concentration gradient across a membrane separating two body compartments. In other words, the drug moves from a region of high concentration to one of lower concentration. The vast majority of drugs are absorbed by this 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 thus, for a weak acid, the uncharged, protonated HA can permeate through membranes, and A− cannot. For a weak base, the uncharged form B penetrates through the cell membrane, but the protonated form BH+ does not. 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, which is represented by the ionization constant, pKa (Figure 1.8). [Note: The pKa is a measure of the strength of the interaction of a compound with a proton. The lower the pKa of a drug, the more acidic it is. Conversely, the higher the pKa, the more basic is the drug.]

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: Reversible binding to plasma proteins sequesters drugs in a non diffusible form and slows their transfer out of the vascular compartment. Albumin is the major drug-binding protein and may act as a drug reservoir (as the concentration of free drug decreases due to elimination, the bound drug dissociates from the protein). This maintains the free drug concentration as a constant fraction of the total drug in the plasma.

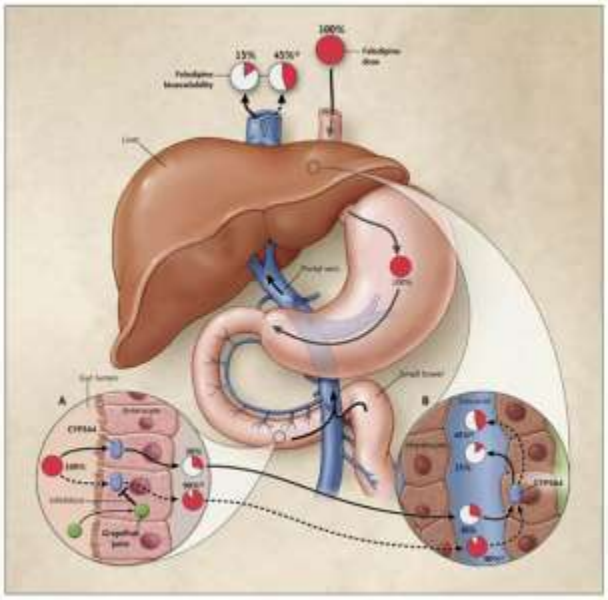
2. Binding to tissue proteins: Many drugs accumulate in tissues, leading to higher concentrations in tissues than in the extracellular fluid and blood

- 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: The apparent volume of distribution, Vd, is defined as the fluid volume that is required to contain the entire drug in the body at the same concentration measured in the plasma. It is calculated by dividing the dose that ultimately gets into the systemic circulation by the plasma concentration at time zero (C0).

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

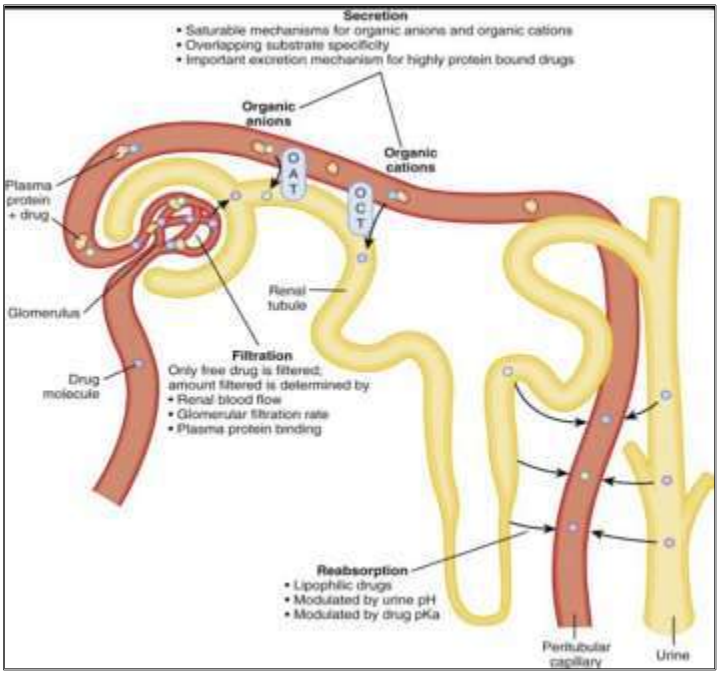


EXCREATION

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.

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Department of anesthesia Pharmacology

Antihypertensive

Lec 2

Lecturer

Faris F. Mohammed

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 β1-adrenoceptors) by releasing the enzyme renin (Figure 17.4). 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

Management of hypertension

1. Diuretics:

Diuretics can be used as initial drug therapy for hypertension

The initial mechanism of action of diuretics is based upon decreasing blood volume, which ultimately leads to decreased blood pressure. Low-dose diuretic therapy is safe, inexpensive, and effective in preventing stroke, myocardial infarction, and heart failure.

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.

Mechanism of action

Loop diuretics inhibit the cotransport of Na+/K+/2Cl− in the luminal membrane in the ascending limb of the loop of Henle. Therefore, reabsorption of these ions is decreased. These agents have the greatest diuretic effect of all the diuretic drugs, since the ascending limb accounts for reabsorption of 25% to 30% of filtered NaCl, and downstream sites are unable to compensate for the increased Na+

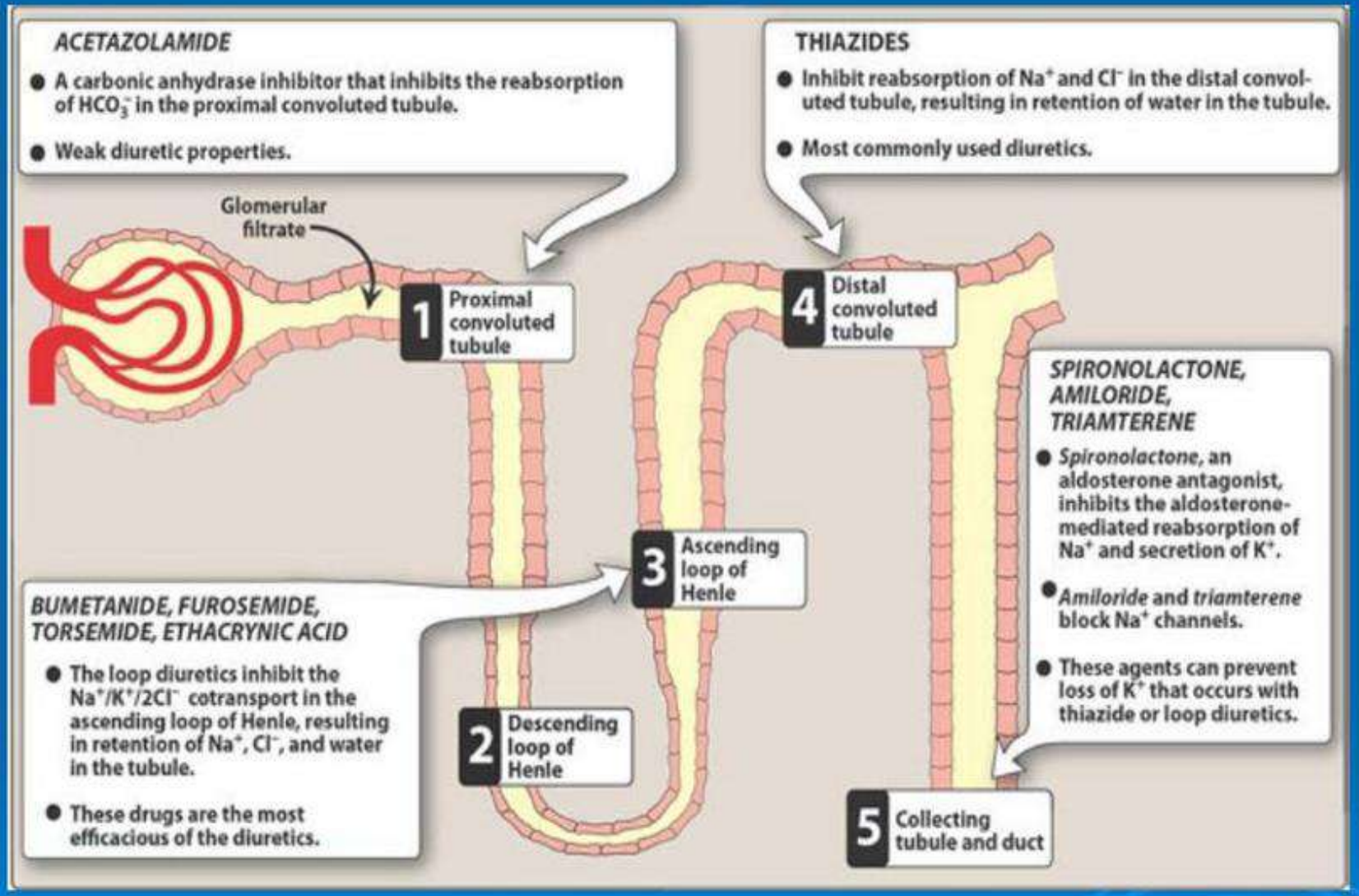

Figure 22.2 Major locations of ion and water exchange in the nephron, showing sites of action of the diuretic drugs.

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 β1, β2)

The nonselective β-blockers, such as propranolol and nadolol, are contraindicated in patients with asthma due to their blockade of β2-mediated bronchodilation.

- Selective (metoprolol, atenolol β1)

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. 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 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.

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.

α-ADRENOCEPTOR–BLOCKING AGENTS

Prazosin, doxazosin and terazosin produce a competitive block of α1-adrenoceptors. They decrease peripheral vascular resistance and lower arterial blood pressure by causing relaxation of both arterial and venous smooth muscle.


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Department of anesthesia

Pharmacology

Practical

2021-2022

Lecturer

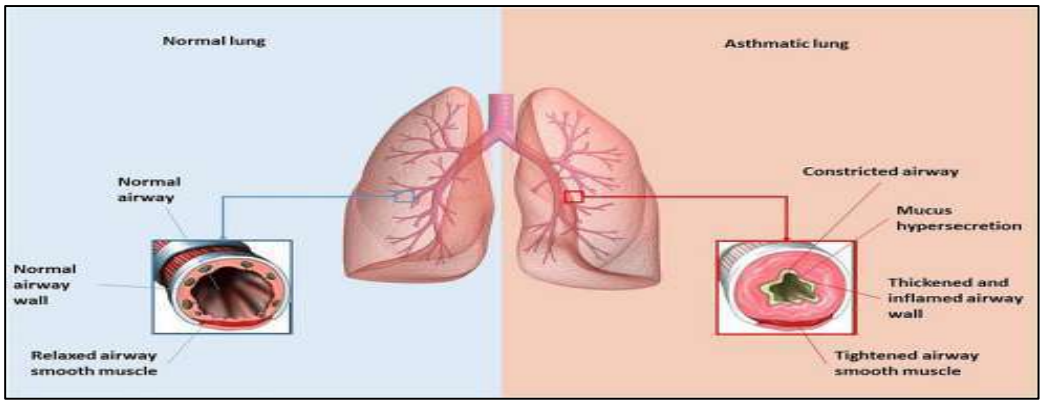
Faris E. Mohammed Lec (3)

Respiratory Disorder

Asthma:

Asthma is a chronic inflammatory disease of the airways characterized by episodes of acute bronchoconstriction causing shortness of breath, cough, chest tightness, wheezing, and rapid respiration. Airflow obstruction in asthma is due to bronchoconstriction that results from contraction of bronchial smooth muscle, inflammation of the bronchial wall, and increased secretion of mucus.

Asthma attacks may be triggered by exposure to allergens, exercise, stress, and respiratory infections. Drug therapy for long term control of asthma is designed to reverse and prevent airway inflammation.



A. β_2 Adrenergic receptor agonists: oral, inhaler

Inhaled β_2-adrenergic receptor agonists directly relax airway smooth muscle. They are used for the quick relief of asthma symptoms, as well as adjunctive therapy for long-term control of the disease.

Short-acting β_2 agonists (SABAs) have a rapid onset of action (5 to 30 minutes) and provide relief for 4 to 6 hours. They are used for symptomatic treatment of bronchospasm, providing quick relief of acute bronchoconstriction.

B_2-selective agonists include

1. Short acting: Salbutamol,
2. Long acting: Salmeterol, Formoterol.

Adverse effect:

- Tachycardia,
- Hypokalemia.
- Hypomagnesaemia.
- Tremor.

B. Corticosteroids:

The drugs of choice for long-term control in patients with any degree of persistent asthma.

Mechanism of action:

- Inhibit the release of arachidonic acid through phospholipase A_2 inhibition, thereby producing direct anti-inflammatory properties in the airways.
- Do not directly affect the airway smooth muscle.
- Decreasing the inflammatory cascade (eosinophils, macrophages, and T lymphocytes), reversing mucosal edema,.
- Decreasing the permeability of capillaries, and inhibiting the release of leukotrienes.

Routes of administration

Inhalation.

Oral.

Adverse effects:

Oropharyngeal candidiasis (due to local immune suppression) and hoarseness. Patients should be instructed to rinse the mouth in a “swish-and-spit” method with water following use of the inhaler to decrease the chance of these adverse events.

C. Alternative drugs. oral

Zileuton, Montilukast:

These drugs are useful for treatment of asthma in patients who are poorly controlled by conventional therapy or experience adverse effects secondary to corticosteroid treatment. These drugs should be used in conjunction therapy for most patients, not as monotherapy.

Mechanism of action:

- Selective and specific inhibitor of 5-lipoxygenase, preventing the formation of both leukotrienes (LTB4) and the cysteinyl leukotrienes (inflammatory mediators).

Adverse effects:

- Elevations in serum hepatic enzymes.
- Headache.
- Dyspepsia.

D. Theophylline: oral, I.V.

Theophylline is a bronchodilator that relieves airflow obstruction in chronic asthma. Theophylline has been largely replaced with β_2 agonists and corticosteroids due to its narrow therapeutic window.

Overdose may cause seizures or potentially fatal arrhythmias.

E. Cholinergic antagonists:

Ipratropium (inhalation)

الأدوية نظري

محاظرة 4

Department of Anesthesia

Pharmacology

Theoretical

2021-2022

Lecturer

Faris E. Mohammed

Lecture 4

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

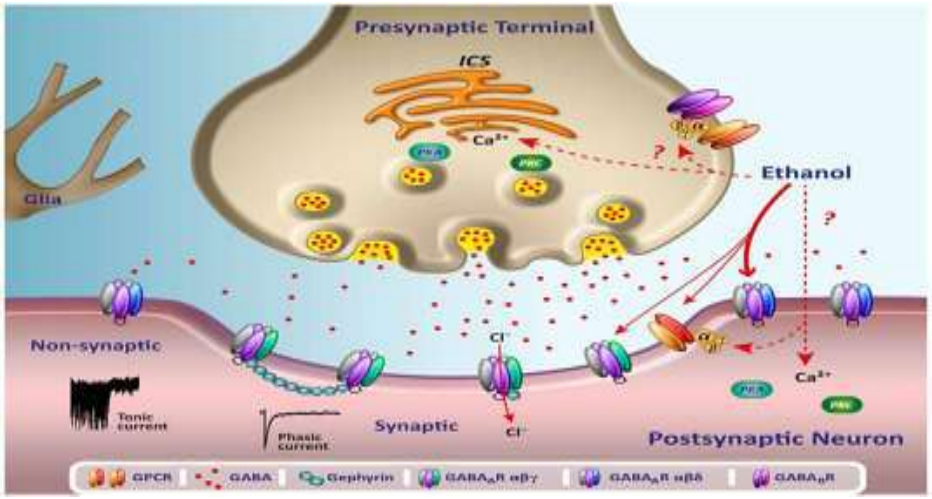
Postoperatively, the anesthetic admixture is withdrawn, and the patient is monitored for return of consciousness. For most anesthetic agents, recovery is the reverse of induction. Redistribution from the site of action (rather than metabolism of the drug) underlies recovery. The patient is monitored 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 Ca2+ 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.

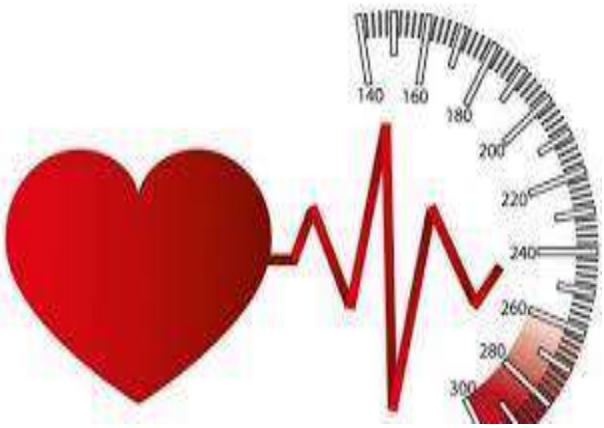
4. **Sevoflurane:**

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.

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Department of Anesthesia Technology

Pharmacology

2021-2022

Lecturer

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Lecture 5

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 remifentanil, 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.