MINISTRY OF EDUCATION AND SCIENCE OF UKRAINE
UZHHOROD NATIONAL UNIVERSITY
FACULTY OF MEDICINE
DEPARTMENT OF BIOCHEMISTRY AND PHARMACOLOGY

REGULATION OF WATER-SALT BALANCE. DIURETICS. ANTIDIURETICS.

Methodical instructions for medical students

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Методичний посібник для студентів складено у відповідності з вимогами освітньо-професійної програми підготовки магістра.

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INTRODUCTION

The main purpose of diuretics, or agents that increase urine output, is to eliminate excess fluid from the body. Introduced into medicine in 1958, diuretics are drugs that increase the excretion of solutes and water by directly increasing urine output. The introduction of potent orally administered diuretics has been one of the most significant therapeutic milestones of the last century. Generally, the primary goal of diuretic therapy is to reduce extracellular fluid volume to decrease blood pressure or to rid the body of excess interstitial fluid (antioedematous effect).

As with all potent agents, rational and safe use of these drugs is predicated on an understanding of their pharmacologic action and their potential side effects.

Learning objective:

1. To get acquainted with the classification of diuretics and their mechanism of action.
2. To get acquainted with the pharmacokinetics and pharmacodynamics of diuretics.
3. To get acquainted with the indications and contraindication of diuretics.
4. To get acquainted with the pharmacological characteristics of antidiuretics.
5. To get acquainted with the pharmacological characteristics of antigout agents.

Questions to prepare:

1. Basic physiological principles of the regulation of water-salt metabolism and the possibility of pharmacological correction. Diuretics and their classification according to the location and mechanism of action by the force of action.
2. Pharmacokinetics and pharmacodynamics of saluretics (saltdriving drugs) - Furosemide, Hydrochlorothiazide, Clopamid, Ethacrynic acid; osmotic diuretics (Mannitol, Urea). Indications and clinical uses, side effects and their prevention. The concept of forced diuresis.
3. Comparative pharmacological characteristics of potassium-sparing drugs spironolactone and triamterene: mechanisms of action, indications, side effects.
4. Features and application of medications that enhance renal blood flow (Theophylline, Minophylline, Xantinole nicotinate, Pentoxifylline).
5. Preparations of medicinal plants that have a diuretic effect: herb Horsetail, Bearberry leaves, leaves Ortosifona, Lespenefril. The principle of the combined using of diuretics.
6. Pharmacological correction of purine metabolism disorders in the body. Classification of antigout agents by the mechanism of action.
7. Comparative pharmacological characteristics of antigout agents (Allopurinol, Etamid, Urolesan, Urodan).

KIDNEY PHYSIOLOGY

Kidney's primary function is to regulate the volume, composition and pH of body fluids. The normally functioning kidney retains substances needed by the body and eliminates those not needed by way of urine.

The nephron is the functional unit of the kidney – each kidney contains approximately 1 million nephrons.

The glomerulus is a network of capillaries and the tubule is a structure of epithelial cells that is divided into 3 main segments – the proximal tubule, loop of Henle and distal tubule – each differing in structure and function.

Urine is a waste byproduct formed from excess water and metabolic waste molecules during the process of renal system filtration.

Urine formation occurs during three processes:

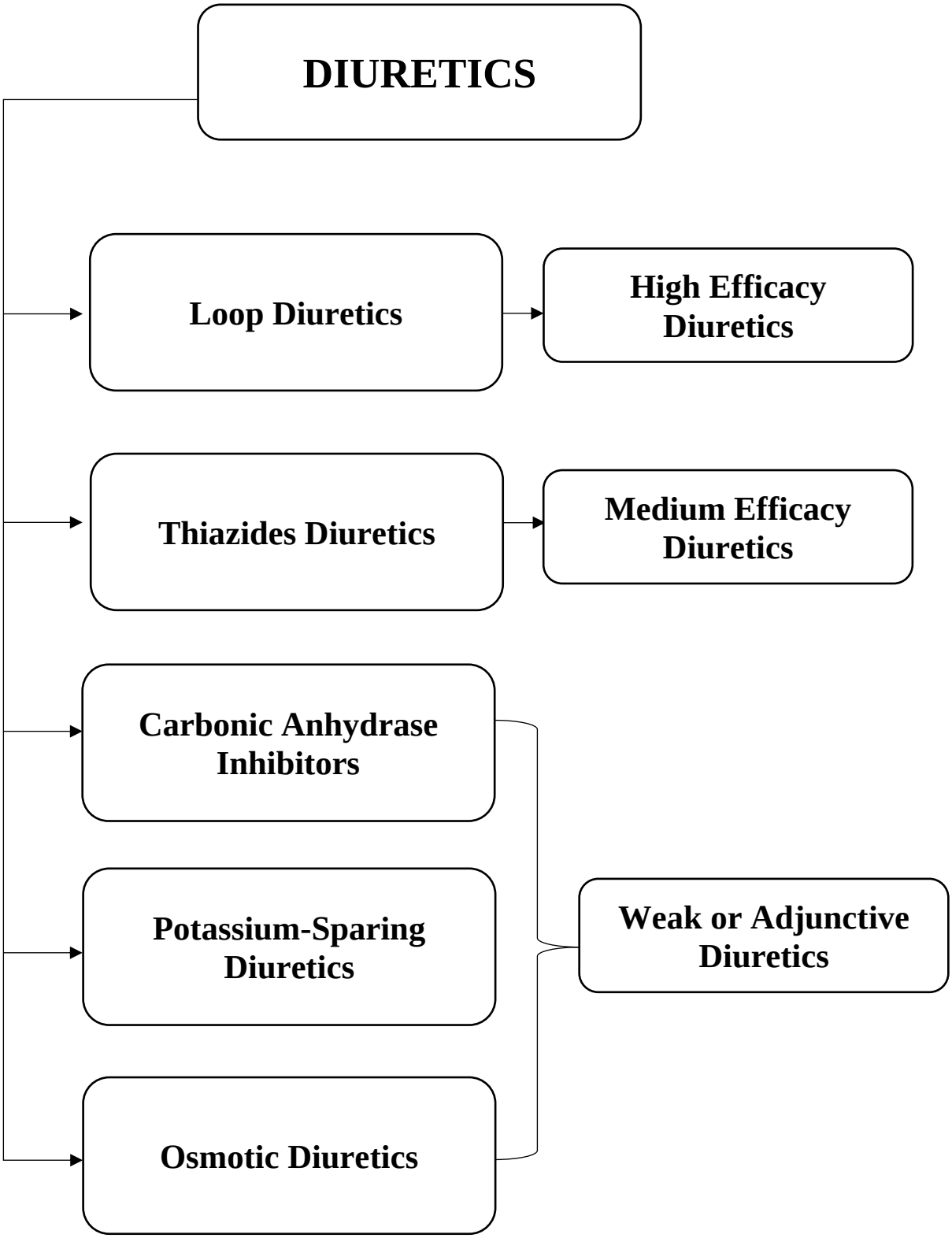
1. Filtration
2. Reabsorption
3. Secretion

During filtration, blood enters the afferent arteriole and flows into the glomerulus where filterable blood components, such as water and nitrogenous waste, will move towards the inside of the glomerulus, and nonfilterable components, such as cells and serum albumins, will exit via the efferent arteriole. These filterable components accumulate in the glomerulus to form the glomerular filtrate.

The next step is reabsorption, during which molecules and ions will be reabsorbed into the circulatory system. The fluid passes through the components of the nephron (the proximal/distal convoluted tubules, loop of Henle, the collecting duct) as water and ions are removed as the fluid osmolarity (ion concentration) changes. In the collecting duct, secretion will occur before the fluid leaves the ureter in the form of urine.

During secretion some substances such as hydrogen ions, creatinine, and drugs—will be removed from the blood through the peritubular capillary network into the collecting duct. The end product of all these processes is urine, which is essentially a collection of substances that has not been reabsorbed during glomerular filtration or tubular reabsorption.

CLASSIFICATION OF DIURETICS



LOOP DIURETICS

Furosemide, Torasemide

FUROSEMIDE

Mechanism of action:

Inhibits the $Na^+/K^+/2Cl^-$ co-transporter in the luminal membrane by combining with the chloride binding site. The mechanism of action loop diuretics is displayed in fig. 1.

Pharmacokinetics:

Given orally (can be given i.v. in emergencies), well absorbed, reaches site of action by being secreted into the proximal tubule. Half-life 90min.

Clinical use:

1. Pulmonary edema
2. Chronic heart failure
3. Ascites due to liver cirrhosis
4. Hypercalcaemia
5. Hyperkalaemia.

Adverse effects: Hypokalaemic alkalosis; hyperuricaemia (can precipitate gout); hypovolaemia and hypotension in elderly patients; reversible ototoxicity.

TORASEMIDE

Another high ceiling diuretic with properties similar to furosemide, but 3 times more potent. Oral absorption is more rapid and more complete. The half-life 3.5 hours and duration of action (4-8 hours) are longer. Torasemide has been used in edema and in hypertension.

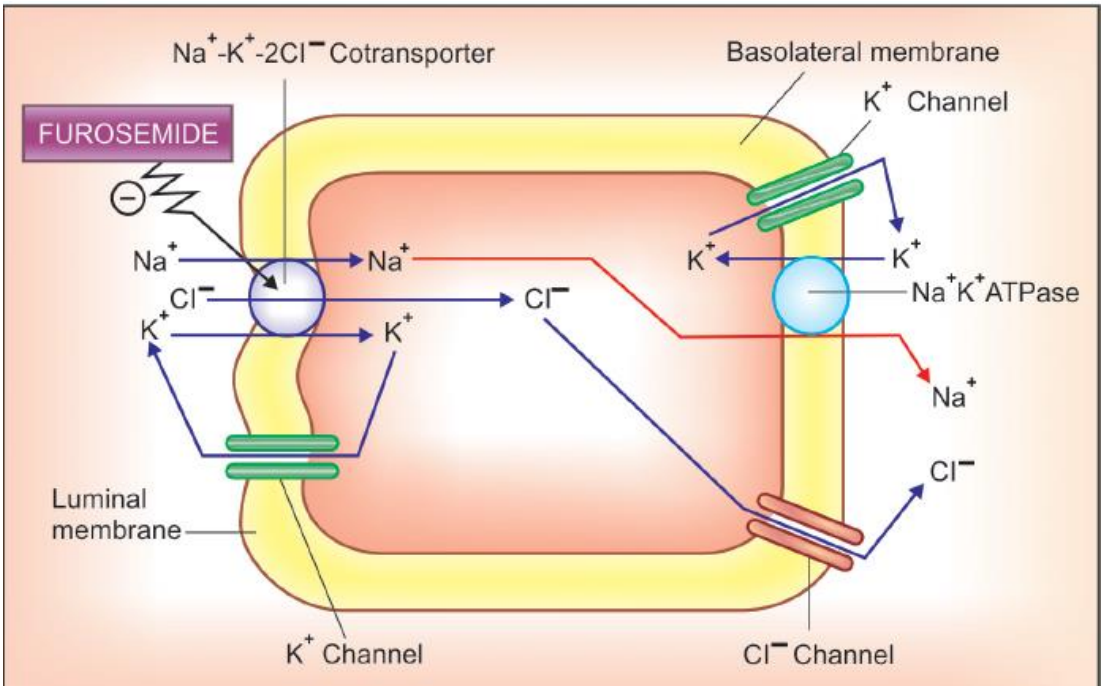


Fig. 1 – Mechanism of action loop diuretics.

THIAZIDES DIURETICS

Hydrochlorothiazide, Chlorthalidone, Metolazone, Indapamide

Mechanism of action: Inhibits the Na^+/Cl^- co-transporter in the luminal membrane of the distal convoluted tubule. The mechanism of action thiazides diuretics is displayed in fig. 2.

Pharmacokinetics:

All thiazides and related drugs are well absorbed orally. There are no injectable preparations of these drugs. Their action starts within 1 hour, but the duration varies from 6-48 hours. The elimination t½ of hydrochlorothiazide is 3-6 hours, but action persists longer (6-12 hours).

Clinical use:

1. Edema
2. Hypertension
3. Diabetes insipidus
4. Hypercalciuria

Adverse effects: Potassium loss; metabolic alkalosis; hyperuricemia (can precipitate gout); increased insulin requirement; erectile dysfunction.

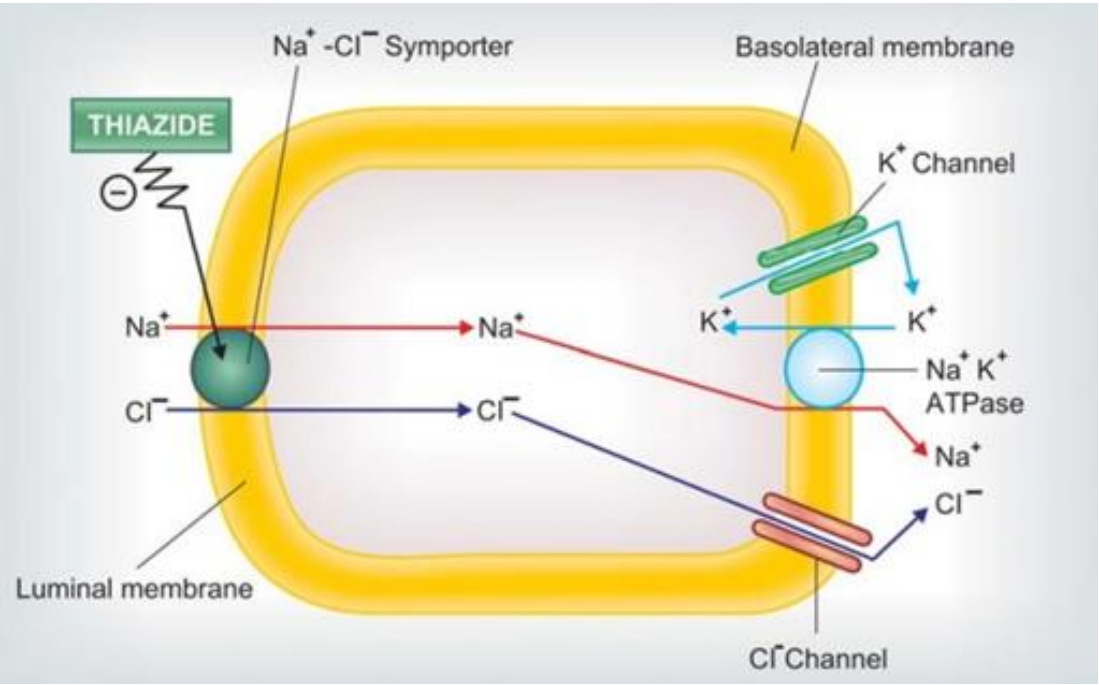


Fig. 2 – Mechanism of action thiazides diuretics.

CARBONIC ANHYDRASE INHIBITORS

Acetazolamide

The diuretic effect of acetazolamide is due to its action in the kidney on the reversible reaction involving hydration of carbon dioxide and dehydration of carbonic acid. The result is renal loss of bicarbonate (HCO3 ion), which carries out sodium, water, and potassium. Alkalization of the urine and promotion of diuresis are the end result.

Pharmacokinetics

Acetazolamide is well absorbed orally and excreted unchanged in urine. Action of a single dose lasts 8-12 hours.

Clinical use:

1. Glaucoma

2. To alkalinize urine

3. Acute mountain sickness

Adverse effects

Acidosis, hypokalemia, drowsiness, paresthesia's, fatigue, abdominal discomfort.

POTASSIUM-SPARING DIURETICS

Aldosterone antagonist: *Spironolactone*

Inhibitors of renal epithelial Na^+ channel: *Triamterene and amiloride*

SPIRONOLACTONE

Mechanism of action:

It is a competitive antagonist of aldosterone; causes diuresis by preventing the production of the aldosterone mediator that normally causes influx of sodium by activating the sodium channel in the luminal membrane of the collecting tubule.

Pharmacokinetics:

Given orally, gives rise to active metabolite, canrenone, which has a plasma half-life of 16h.

Clinical use:

1. Hypertension, given with K^+-losing diuretics (thiazides, loop diuretics) to limit K^+ loss.

2. Primary and secondary hyperaldosteronism.

Adverse effects: Hyperkaliemia; hyperchloremic acidosis. Can cause gynecomastia.

TRIAMTERENE AND AMILORIDE

Mechanism of action:

Inhibits the sodium channel in the luminal membrane of the collecting tubule, reducing sodium influx.

Pharmacokinetics:

Given orally. Triamterene has more rapid onset and shorter duration of action than amiloride

Clinical use:

Given with K^+-losing diuretics (thiazides, loop diuretics) to limit K^+ loss.

Adverse effects: Hyperkaliemia; may cause acidosis.

OSMOTIC DIURETICS

Mannitol

Mechanism of action:

It is an inert compound that passes across into the filtrate at the glomerulus and is not reabsorbed. Acts in those parts of the nephron that are freely permeable to water.

Pharmacokinetics:

Given intravenously, not metabolized, excreted in about 30min.

Clinical use:

1. Cerebral edema

2. Increased intraocular pressure

Adverse effects:

Temporary expansion of the extracellular fluid compartment and hyponatremia due to osmotic extraction of intracellular water. Pulmonary edema may occur.

ANTIDIURETICS

Are drugs that reduce urine volume, particularly in diabetes insipidus which is their primary indication.

1. Antidiuretic hormone (ADH, Vasopressin), Desmopressin, Lypressin, Terlipressin
2. Thiazide diuretics, Amiloride.
3. Miscellaneous: Indomethacin, Chlorpropamide, Carbamazepine.

VASOPRESSIN

Mechanism of action: binds to V_2 receptors on the cell surface of tubular cells, initiating an intracellular cascade which results in the generation of the water channel, aquaporin-2. Preformed aquaporin-2 also migrates and inserts into the luminal membrane of the tubule cells, where it acts as a conduit for water to be reabsorbed from the urine, through the cell, and back into the circulation. This leads to a decrease in renal free water clearance, the concentration of urine, and a reduction in urine volume. The net effect is the reabsorption of water into the blood, which, along with thirst-generated water intake, leads to the normalization of plasma osmolality.

Pharmacokinetics: inactive orally because it is destroyed by trypsin. It can be administered by any parenteral route or by intranasal application. The peptide chain of Arginine Vasopressin is rapidly cleaved enzymatically in many organs, especially in liver and kidney; plasma half-life is short ~25 min. However, the action of aqueous vasopressin lasts 3-4 hours.

Clinical use: indicated to increase blood pressure in adults in vasodilatory shock refractory to the application of fluids and catecholamines. Diabetes insipidus.

Adverse effects: Allergic reaction, bronchial constriction, chest pain (angina), decreased cardiac output.

DRUGS USED IN TREATMENT OF GOUT

Gout it is a metabolic disorder characterized by *hyperuricaemia* (normal plasma urate 2-6 mg/dl). Uric acid, a product of purine metabolism (Fig.3), has low water solubility, especially at low pH. When blood levels are high, it precipitates and deposits in joints, kidney and subcutaneous tissue (tophy).

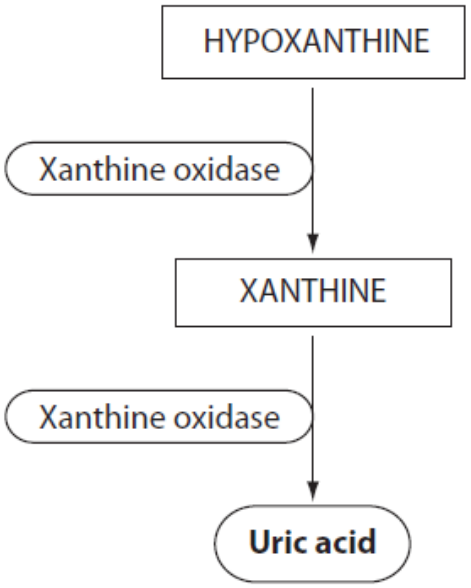


Fig.3 – Metabolic pathway in the production of uric acid.

Drugs used in gout are:

For acute gout:

1. NSAIDs
2. Colchicine
3. Corticosteroids

For chronic gout/hyperuricaemia:

Uricosurics (They promote renal excretion of uric acid): Probenecid, Sulfinpyrazone;

Uricostatics (Synthesis inhibitors): Allopurinol, Febuxostat.

PROBENECID

Mechanism of action: inhibits the tubular reabsorption of urate, thus increasing

the urinary excretion of uric acid and decreasing serum urate levels.

Pharmacokinetics: Probenecid is completely absorbed orally; 90% plasma protein bound: partly conjugated in liver and excreted by the kidney; half-life period is 6-8 h.

Clinical use: Chronic gout and hyperuricaemia; also used to prolong penicillin or ampicillin action by enhancing and sustaining. Their blood levels.

Adverse effects: Dispepsia

ALLOPURINOL

Mechanism of action: Inhibits xanthine oxidase and also the biotransformation of purines to xanthine.

Pharmacokinetics: Given orally; well absorbed; converted to alloxanthin which has a half-life of 18-30 h and is the moiety that inhibits xanthine oxidase.

Clinical use: To prevent episodes of gout.

Adverse effects: Gastrointestinal disturbances. Rashes and blood dyscrasias can occur.

LIST OF DIURETICS RECOMMENDED FOR EXAM PREPARATION

Name in English	Name in Latin	Drug forms
Hydrochlorothiazide	*Hydrochlorothiazidum*	tab.25 mg; 100 mg
Indapamide	*Indapamidum*	tab.1,5 mg; 2,5 mg
Spironolactone	*Spironolactonum*	tab.25 mg; 50 mg; 100 mg
Torasemide	*Torasemidum*	amp.5 mg/1 ml, tab.10 mg
Furosemide	*Furosemidum*	tab.40 mg, amp.10 mg/ml
Allopurinol	*Allopurinolum*	tab.100 mg; 300 mg

PRESCRIPTIONS

1. Prescribe 10 tablets of Spironolactonum, each tablet 25 mg. Take 1 tablet once a day.
2. Prescribe 10 ampoules with solution of Furosemidum, 10 mg/ml (1 ampoule – 2 ml). For IV injection.
3. Prescribe 10 tablets of Hydrochlorothiazidum, each tablet 25 mg. Take 1 tablet twice a day.
4. Prescribe 10 tablets of Torasemidum, each tablet 10 mg. Take 1 tablet once a day.
5. Prescribe 10 tablets of Indapamidum, each tablet 2,5 mg. Take 1 tablet once a day.
6. Prescribe 50 tablets of Allopurinolum, each tablet 100 mg. Take 2 tablet twice a day.

Tests for Self-assessment:

1. A patient suffers from acute cardiopulmonary failure with pulmonary edema. What diuretic should be prescribed in the given case?

A. Furosemide

B. Triamterene

C. Spironolactone

D. Hydrochlorothiazide (Dichlothiazidum)

E. Acetazolamide (Diacarb)

2. A 65-year-old female patient suffers from chronic renal insufficiency accompanied by evident edemata caused by chronic glomerulonephritis. What diuretic should be administered for forced diuresis?

A. Acetazolamide

B. Hydrochlorothiazide

C. Chlorthalidone

D. Cyclometazide

E. Furosemide

3. A patient takes digoxin for treatment of cardiac insufficiency. What diuretic may increase digoxin toxicity due to the intensified excretion of K+ ions?

A. Lisinopril

B. Hydrochlorothiazide

C. Panangine

D. Siliborum

E. Spironolactone

4. A patient with chronic cardiac insufficiency has been treated with cardiotonic drugs and a thiazide diuretic, but in spite of it there are still edemata and risk of ascites. What medication should be prescribed to amplify diuretic effect of the applied drugs?

A. Spironolactone

B. Manitole

C. Amyloride

D. Clopamide

E. Furosemide

5. Diuretic drug was prescribed to the patient with hypertension in the course of complex treatment. In a few days BP decreased but signs of hypokaliemia developed. What drug could cause such complications?

A. Clopheline

B. Spironolactone

C. Lasix

D. Triamterene

E. Enalapril

6. The alternate usage of dichlotiazide, etacrin acid and lasex didn't cause marked diuretic effect in patient with marked peripheral edema. Increased amount of aldosterone is in the blood. Indicate the medicine to be prescribed.

A. Mannitol

B. Spironolacton

C. Clopamid

D. Urea

E. Amilorid

7. A 75-year-old pharmacologist comes to the emergency department because of chest pain and shortness of breath. She has a history of hypertension. She says that she takes an aspirin daily and a diuretic that “acts at the distal tubule of the nephron.” She cannot remember the name of the diuretic. Considering her description, which of the following is the most likely diuretic?

A. Ethacrynic acid

B. Furosemide

C. Spironolactone

D. Mannitol

E. Hydrochlorothiazide

8. A patient with essential hypertension is starting diuretic therapy. He has a history of calcium oxalate renal stones. Which of the following diuretics would be most

appropriate for this patient?

A. Acetazolamide

B. Hydrochlorothiazide

C. Furosemide

D. Spironolactone

E. Triamterene

9. On a routine annual examination, a previously healthy 59-year- old woman is found to have high blood pressure. Her high blood pressure is confirmed on three subsequent visits. She tries to control it with diet and exercise, but 1 year later it is still elevated and so she is given a prescription for a diuretic. She returns for a follow-up visit, and laboratory studies show an elevation of her potassium levels. She was most likely prescribed which of the following diuretics?

A. Acetazolamide

B. Triamterene

C. Hydrochlorothiazide

D. Metolazone

E. Furosemide

10. From the mentioned below choose the drug which acts on the level of basolateral membrane.

A. Chlorthiazide

B. Triamteren

C. Amilorid

D. Spironolactone

E. Eplerenone

LIST OF INFORMATION SOURCES

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