I. Diuretics

Classification of diuretics

- Inhibitors of carbonic anhydrase
- Osmotic diuretics
- Inhibitors of Na+/K+/Cl- symport (loop diuretics, high-ceilling diuretics)
- Inhibitors of Na+/Cl- symport (thiazides and thiazide-like diuretics)
- Inhibitors of renal epithelial Na+ channels (K+ - sparing diuretics)
- Antagonists of mineralocorticoid receptors (aldosterone antagonists, K+ - sparing diuretics)

Inhibitors of carbonic anhydrase

Mechanism of action

Inhibit carbonic anhydrase activity in proximal and distal convoluted tubule.

Pharmacological profile

- Increase urinary excretion of HCO_3^- , ↑urinary pH, metabolic acidosis in blood
- Increase delivery of Na^+ and K^+
- Produce hyperchloremic acidosis
- Induce excretion of phosphates
- Decrease production of HCO_3^- in aqueous humor
- Induce metabolic acidosis in CNS
- Reduce gastric acid secretion

Indications: glaucoma, urinary alkalization, metabolic alkalosis, severe hyperphosphatemia, mountain sickness syndrome, hypo- and hyperkalemic periodic paralysis, epilepsy

Contraindications: hepatic encephalopathy, severe acidosis, hyponatremia and hypokalemia

Adverse effects: like sulfonamides – allergy, bone-marrow depression, renal lesions, drowsiness and paresthesias, calculus formation

Examples: acetazolamide, dorzolamide

Loop diuretics

Mechanism of action

Inhibit Na+/K+/Cl- symport in thick asceding limb of the loop of Henle.

Pharmacological profile

- increase excretion of Na^+, Cl^-, K^+, Ca^{2+}, Mg^{2+}, HCO_3^- , phosphates, uric acid excretion ↓, ↑RBF and GFR, ↑ renin release, ↑ venous capacitance

Adverse effects: dehydration, dyselectrolitemia, thromboembolic episodes, hypochloremic alkalosis, ototoxicity, hyperuricemia, hyperglycemia, hyperlipidemia

Therapeutic uses: acute pulmonary edema, chronic congestive heart failure, hypertension, nephrotic syndrome, chronic and renal insufficiency, hepatic insufficiency, forced diuresis, life-threatening hyponatremia

Contraindications: hyponatremia, severe volume depletion, hypersensitivity to sulfonamides, anuria

Examples: sulfonamide- based – furosemide, bumetanide; phenoxyacetic acid derivative – ethacrinic acid, sulfonylurea – torsemide

Thiazide and thiazide-like diuretics

Mechanism of action

Inhibit Na+/Cl- symport in renal distal convoluted tubule.

Pharmacological profile

- like loop diuretics, excluding ↑ Ca^{2+} reabsorption, reduced GFR

Indications: congestive heart failure, hypertension, calcium nephrolithiasis, osteoporosis, nephrogenic diabetes insipidus, Br^- intoxications

Contraindications: hyponatremia, severe volume depletion, anuria, diabetes mellitus, hyperlipidemia, renal insufficiency

Adverse effects: abnormalities of fluid and electrolyte balance, impotence, hyperglycemia, hyperlipidemia, neurological and gastrointestinal symptoms, blood dyscrasias

Examples: hydrochlorothiazide, chlortalidone, indapamide

Osmotic diuretics

Mechanism of action

Pull water into the vascular space through their osmotic concentrations; the water is then excreted in the urine.

Act along whole nephron, the major site of action are: the loop of Henle and the proximal tubule

Pharmacological profile

General features:

- Freely filtered at the glomerulus
- Undergo limited reabsorption

Are relatively inert pharmacologically.

Osmotics result in:

- volume depletion, increased excretion of almost all electrolytes, decreased blood viscosity, increased RBF and GFR

Indications: acute renal insufficiency, intoxications, cerebral edema – prophylaxis
Contraindications: left-ventricular cardiac insufficiency, chronic renal insufficiency, established anuria
Adverse effects: dehydration and dyselectrolitemia, pulmonary edema, hyponatremia, urea - trombosis or pain in site of injection, hepatic failure, hyperglycemia - glycerin
Examples: urea, mannitol, glycerin

Inhibitors of renal epithelial Na+ channels

K+ – sparing diuretics
Mechanism of action
Inhibit renal epithelial Na+ channels in distal convoluted tubule and collecting duct system.
Pharmacological profile
- mild influence on blood volume, ↓excretion of K+, H+, Ca2+, Mg2+, uric acid; cause metabolic acidosis

Indications: edema, hypertension, but in combination with thiazides or loop diuretics, cystic fibrosis – amyloride, lithium- induced diabetes insipidus
Contraindications:hypersensitivity, anuria, renal insufficiency
Adverse effects: hyperkalemia, GI disturbances
Triamterene– folic acid antagonist
Triamterene - reduces glucose tolerance
Triamterene – interstitial nephritis and nephrolithiasis
Examples: amyloride, triamterene

Aldosterone antagonists

Antagonists of mineralocorticoid receptors
K+ – sparing diuretics
Mechanism of action
Compete with aldosterone in binding with its receptor
Pharmacological profile
- mild influence on blood volume, ↓excretion of K+, H+, Ca2+, Mg2+ , uric acid, cause metabolic acidosis

Indicationss: edema and hypertension to prevent hypokalemia (in combination with other diuretics), primary and secondary hyperaldosteronism
*Contraindications:*pregnancy, lactation
Adverse effects: hyperkalemia, gynecomastia, impotence, decreased libido, hirsutism, deepening of the voice, menstrual irregulations, diarrhea, gastric bleeding
Examples: spironolactone, eplerenone

II. Antidiuretic hormone antagonists

Lithium and demeclocycline
Mechanism of action
reduce cAMP formation in response to ADH in collecting tubule and interfere with cAMP
Pharmacological profile
- inhibit the effect of ADH secretion

Indications: SIADH
Contraindications: demeclocycline – liver failure, lithium – hypothyroidism, renal insufficiency
Adverse effects: nephrogenic diabetes insipidus, severe hypernatremia, acute renal failure, lithium – mental obtundation, cardiotoxicity, thyroid dysfunction, leukocytosis

Conivaptan and tolvaptan
- Conivaptan blocks both V_{1A} and V_2 receptors, tolvaptan is V_2 selective.
- The V_2 receptors are coupled with insertion of aquaporin channels in the apical membranes of the renal collecting ducts, leading to reabsorption of water (antidiuretic effect).
- By activating these receptors, antidiuretic hormone helps maintain plasma osmolality in the normal range.
- Antagonism of V_2 receptors by conivaptan and tolvaptan causes free water excretion or aquaresis, and the drugs are called aquaretics.
- Dehydration, hypokalemia, orthostatic hypotonia