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MAIN REPRESENTATIVES OF OSMOTIC DIURETICS AND PRINCIPLE OF THEIR ACTION

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Hydrouretics, or osmotic diuretics, increase water diuresis (loss of water in the urine) due to high osmotic activity. Osmotic diuretics have very strong diuretic and decongestant properties (sometimes even superior to loop diuretics), but only in patients with normal glomerular filtration rate. The main representative of this group – mannitol – is most often used to reduce swelling of the brain and spinal cord of various origins, in the complex therapy of traumatic brain injuries and spinal injuries, volumetric (including malignant) formations of the central nervous system, as well as to control intraocular pressure in some ophthalmic operations. The main mechanism of the diuretic action of osmodiuretics is a significant decrease in the reabsorption of sodium ions in the distal nephron. The presence of a substance with high osmotic activity in the lumen of the collecting tubules leads to water retention and a drop in the intraluminal concentration of Na^+ ions, a sharp decrease in its reabsorption, and, moreover, to the absorption of sodium ions from the peritubular space. All this occurs against the background of an increase in blood flow in the renal medulla, which is due to the vasodilating effect of osmodiuretics. At the same time, there is a "washout" of the normal hypertonicity of the medullary interstitium of the kidneys and, as a result, a decrease in sodium reabsorption in the thin ascending section of the loop of Henle. Ultimately, the production of secondary urine increases against the background of a relatively low excretion of sodium ions, since the main diuretic effect is due to an increase in urine production.

Keywords: diuretics, osmodiuretics, mannitol, urea, chronic heart failure, arterial hypertension, chronic renal failure, nephron

Introduction

Diuretics in the medical environment are known as a class of medicines, the principle of action of which is aimed at providing forced diuresis, in other words, removing excessive amounts of mineral and organic salts, water from the body and eliminating edematous syndrome. The functional activity of diuretics is revealed in the nephron, the morphofunctional unit of the kidney. Primary urine is filtered from blood plasma in the nephron capsule, after which a further process of secondary urine formation takes place in the tubular apparatus of the nephron by reabsorption and secretion of various secreted substances into the urine. As a result of these processes, the volume of urine increases by 2 times with a decrease in the rate of reabsorption by only 1%. It is known that drugs with even a minor effect on the processes of reverse absorption of electrolytes in the renal tubules have the ability to cause a significant change in diuresis. The excretion of biochemically significant ions for the body (magnesium, potassium, chlorine, phosphates and bicarbonates) is one of several side effects of diuretic drugs. At the same time, the reverse situation is also possible, when pathological processes leading to a temporary or permanent change in the structure of the glomeruli and tubules can cause serious changes in the water and electrolyte balance in the body.

Osmotic diuretics are understood to be a group of drugs with a pronounced osmotic effect that are freely filtered by the glomerular apparatus of the kidneys, while being inert from a pharmacological point of view, as a result of which they undergo little or practically no reabsorption. Drugs of this pharmacological group have an effect on osmotic pressure by increasing the osmolality of blood plasma within 10 mOsm / kg. At the same time, diuretic drugs have a complex effect on systemic and organ hemodynamics, indirectly regulating the state of electrolyte balance and some metabolic processes. Among the representatives of osmodiuretics, a special place is occupied by the hexatomic alcohol mannitol, the scope of application of which in clinical medicine is very extensive: from combating brain oedema, increasing intracranial pressure in neuro–intensive care and neurosurgery, prevention and early therapy of acute renal failure of ischemic and toxic gen-

esis, to an antioxidant – for the prevention of ischemic and reperfusion disorders in cardiac surgery, vascular surgery, cardiology. Other representatives of the diuretic series are also known, including sorbitol, isosorbide, glycerine, and urea. Nowadays, they have found a narrow scope of application and are more often last-line drugs, due to a wide range of side effects and complications [1].

Relevance. In clinical practice, a lot of experience has been accumulated in the use of diuretic drugs, the beginning of widespread use of which dates back to 60-70 of the XX century. The first representatives of this class of drugs were mercury diuretics and carbonic anhydrase inhibitors. Today, diuretic drugs are presented much more widely, new groups have appeared, and new representatives in the groups of diuretics, in the synthesis of which the undesirable clinical properties of their predecessors were taken into account. All diuretics are divided into five groups, depending on the effect on different parts of the nephron.

The first group consists of diuretics acting on the proximal convoluted tubules. These include carbonic anhydrase inhibitors and osmotic diuretics. At the same time, osmotic diuretics (lure, urea) are characterized primarily by a dehydration effect, which determines the possibility of their clinical use [2].

The second group is represented by diuretics acting on the distal tubules. These include thiazide and thiazide-like diuretics. The first generation of thiazide diuretics is represented by hydrochlorothiazide (hypothiazide, disalunil, ezidrex; daily dose 25-50 mg) and chlorthalidone (hygroton, oxazoline; daily dose 15-30 mg). These drugs are characterized by a moderate natriuretic and diuretic effect, a high antihypertensive effect, and a long-lasting effect, which allows them to be widely used in the treatment of arterial hypertension and edematous syndrome. In addition, thiazide diuretics reduce the excretion of calcium ions in the urine, which makes it possible to give preference to these drugs in patients with concomitant osteoporosis [3].

The third group is diuretics acting on the ascending loop of Henle, or loop diuretics. They, like the previous group, are represented by two generations. The first generation is short-acting loop diuretics: furosemide (lasix, daily dose 20-320 mg), ethacrynic acid (uregit, edecrine daily dose 25-100 mg), bumetanide (bufenox, bumex, daily dose 0.5-5 mg). A feature of these drugs is a pronounced, powerful diuretic and natriuretic effect. Moreover, these effects are dose-dependent, the drugs are characterized by a large range of therapeutic doses, and its increase is accompanied by an increase in diuresis. The second generation – long-acting loop diuretics is represented by torasemide (trifas daily dose of 5-20 mg). The peculiarity of the drug is that it is a modern loop diuretic, not inferior, and even superior in efficiency to short-acting loop diuretics [2].

The fourth group – diuretics, acting mainly on the glomerulus, are represented by aminophylline (eufillin) and theobromine. Currently, actually as diuretics are rarely used, for example, eufillin finds its application in some clinical situations in obstetrics, nephrology, pulmonology [4].

The fifth group – diuretics, acting mainly in the area of the collecting ducts. This group has another definition – potassium-sparing diuretics. Representatives of this group include spironolactone (veroshpiron, aldactone, spiro, spironol, daily dose of 25-400 mg), amiloride (mizamor, arumil, daily dose of 5-20 mg), triamterene (zaitek, pterofen, daily dose of 50-200 mg), eplerenone (inspra, daily dose 25-50 mg). This group of drugs finds its application in the treatment of edematous syndromes of combination therapy. The combination with loop or thiazide diuretics allows to achieve a more pronounced diuretic effect and reduce potassium losses. Representatives of this group, in particular spironolactone, are pathogenetically justified in the treatment of edematous syndrome against the background of portal hypertension [2]. **Purpose of research.** To study the list of Russian and foreign sources describing the features of the main representatives of several osmotic diuretics, their scope and purpose.

Materials and methods of research

To study the basic data on the pharmacological characteristics of osmotic diuretics, as well as the methods of their functional application, we have developed a list of Russian and foreign sources.

Research results and their discussion

Osmotic diuretic drugs – mannitol, sorbitol, urea – increase the osmotic pressure of blood plasma. These drugs, due to their filtration in the glomeruli of the nephron, enter the primary urine. From the inner space of the nephron, osmotic diuretics are practically not reabsorbed. Their presence in the primary urine increases its osmotic pressure, inhibits water reabsorption, and consequently, diuresis increases. The presence of osmotic diuretics in the circulating blood increases the circulating blood volume. The increased blood volume activates specific

(endothelial) cells of the atria and liver, which provide the release of natriuretic peptide, which inhibits sodium reabsorption in the renal tubules, thereby achieving increased diuresis [1].

Pharmacokinetics: osmotic diuretics are administered intravenously slowly by stream or drip. Mannitol – almost completely remains in the bloodstream (a dehydrating effect is observed in children), but a certain amount of it – up to 10% – penetrates into tissue cells. Sorbitol and urea penetrate the tissues in large quantities. Sorbitol can be metabolized to glycogen. Urea quite freely penetrates into the tissues of the body and for a long time, retaining in them, maintains their high osmotic pressure, which retains fluid in the tissues (the rebound effect). The diuretic effect of osmotic diuretics occurs almost immediately (after 10-15 minutes). The duration of the diuretic action lasts up to 4-6 hours and depends on the completeness of the withdrawal of the active pharmacological agent.

Pharmacodynamics: increased diuresis; a slight initial increase in blood pressure (due to a slight post-infusion increase in BCC). Osmotic diuretics in the proximal tubules increase the osmotic pressure of the primary urine, which causes relative fluid retention in the primary and then in the final urine [2].

Side effects: headache, nausea, vomiting. When it enters the subcutaneous tissue, it causes haemorrhages and tissue necrosis. Osmotic diuretics increase the permeability of the blood-brain barrier to other drugs and bilirubin – which can lead to bilirubin encephalopathy. The effect of rebound and increase in the level of residual nitrogen (due to urea) is also undesirable.

Mannitol (mannitol) is a six-hydric alcohol.

Urea for injection (urea) is a specially purified, sterilized, lyophilized powder.

Indications:

• drug poisoning (barbiturates, salicylates, sulfonamides, PAS, boric acid); hemolytic poisons (acetic and oxalic acid, antifreeze); transfusion of incompatible blood. Contribute to the alkalization of urine – prevent the coagulation of proteins, which means they prevent blockage of the renal tubules,

• toxic pulmonary oedema (poisoning with gasoline, kerosene, turpentine, formalin),

• fluid retention in case of poisoning with non-steroidal anti-inflammatory substances (when loop diuretics are ineffective),

• burns, sepsis, peritonitis, osteomyelitis – improve the excretion of toxic substances, increase low blood pressure [3].

Osmotic diuretics are considered effective and adequately dosed if the increase in diuresis is more than 50 ml per 1 m^2 of body surface per hour.

In clinical practice, in the presence of tissue oedema (due, as a rule, to the retention of Na^+ ions), it is first of all necessary to increase the excretion of sodium ions, and osmotic diuretics, unfortunately, are weak saluretics; that is why they are rarely used as diuretics. They are prescribed mainly for dehydration in combination with other diuretics to force diuresis. Sometimes osmotic diuretics are used to prevent acute kidney failure: by increasing blood volume, they reduce the relative oncotic pressure of the blood serum, inhibit reabsorption, which increases glomerular filtration to a certain extent, which increases diuresis. Osmotic diuretics act throughout the tubular apparatus of the kidney. Mannitol is mainly used as an osmotic diuretic. Mannitol, unlike urea, does not penetrate cell membranes, the blood-brain barrier, and does not increase the content of residual nitrogen in the blood [2].

Side effects. Osmotic diuretics can disrupt water-salt metabolism, causing hyponatremia, hyperazotemia, especially in patients with kidney and liver failure, as well as in the presence of circulatory failure. Due to the fact that urea is partially reabsorbed (up to 50%) and is able to penetrate into the cells, with cerebral oedema, urea can cause rehydration of the cells. With insufficient heart function, an increase in the volume of circulating blood with osmodiuretics makes it difficult for the myocardium to work and somewhat worsens the patient's condition.

In the clinic, mannitol is most often used to relieve oedematous syndrome of the brain and treat intracranial hypertension in patients after severe TBI and with volumetric formations of the central nervous system. At the same time, it is recommended to administer mannitol in the form of a rapid intravenous infusion of 20% solution for 15-30 minutes, the average dose of the drug is 0.5-1 g / kg of body weight. In this case, it is preferable to use a bolus (discrete) administration of mannitol, which reduces the incidence of the "recoil" phenomenon in comparison with the constant infusion of large doses of mannitol. Like all osmodiuretics, mannitol is advisable to use to temporarily reduce cerebral oedema and reduce ICP, provided that the administration of this drug is followed by more radical and effective therapeutic measures that, if possible, eliminate the cause of cerebral oedema and intracranial hypertension, surgical interventions are most often performed [4].

Osmodiuretics are widely used in neurosurgical interventions, especially in deep brain tumors, to control intracranial pressure, reduce

oedema and swelling of the brain, and improve conditions for surgical access. As previously mentioned, mannitol is administered as an intravenous infusion of 20% solution for 15-30 minutes immediately after the start of general anaesthesia, with adequate monitoring of hemodynamics and electrolyte balance parameters. The clinical effect develops 15 minutes after the start of the infusion and lasts 1.5-6 hours. Mannitol has been shown to be effective in reducing intraoperative retraction ischemia. Moreover, mannitol can be considered as a promising cerebroprotector in various types of neurovascular interventions – carotid endarterectomy, temporary clipping of cerebral arteries during operations for arterial aneurysms, and also as a component of the treatment of ischemic strokes accompanied by the development of secondary cerebral oedema [3].

There is an assumption about the practical use of mannitol in the chemotherapy of CNS tumors, due to the possibility of a short-term violation of the integrity of the blood-brain barrier under the influence of significant doses of mannitol, resulting in a temporary increase in the permeability of the blood-brain barrier for a number of antitumor substances, including methotrexate, cisplatin, CCNU.

Mannitol has also found practical application in ophthalmology. Here, due to effective control of the level of intraocular pressure, it is used to temporarily reduce intraocular pressure during various ophthalmic surgical interventions in patients with open-angle glaucoma [4].

Mannitol has shown its effectiveness in the prevention and early treatment of acute renal failure of ischemic and toxic origin. In the first and in the second variant, a decrease in diuresis is associated either with a decrease in the level of glomerular filtration, or a change in permeability in the tubular apparatus of the kidneys under the action of a toxic agent. When an osmodiuretic enters the lumen of the renal tubules, water reabsorption decreases sharply and the concentration of a toxic substance drops, and early administration of mannitol reduces the potential damaging effect of a toxic agent. In oliguric states, accompanied by a sharp drop in glomerular filtration, almost all the water that reaches the distal nephron is reabsorbed. But in the presence of an osmotic agent, the filtration of which changes little, the degree of water reabsorption decreases and, although limitedly, the production of secondary urine is maintained [5].

With a relatively short ischemia of the kidneys, the nephron walls are impermeable to mannitol, but with prolonged ischemia with the development of acute tubular necrosis or a high concentration of nephrotoxic substances that damage the tubular epithelium, the selective permeability of the nephron walls for water molecules gradually decreases, which makes the use of osmodiuretics ineffective. As already mentioned, mannitol has certain vasodilator properties. Indeed, at medium to low doses of mannitol (< 200 mg per day or < 400 mg in 48 hours), mannitol causes severe dilatation of the arteries and arterioles of the kidneys. At the same time, there is a significant increase in renal blood flow, primarily in the medulla, which is especially sensitive to ischemia. The mechanism of this phenomenon seems to be associated with a mannitol-induced increase in the production of prostaglandins in the medullary apparatus of the kidneys [6]. In the oliguric form of acute renal failure, a test dose of mannitol is usually administered first – 1-2 mg / kg of a 20% solution as an intravenous infusion over 20-30 minutes. If a urine output of more than 30-50 ml per hour cannot be achieved after administration of a test dose or a repeated dose of mannitol after 1-3 hours, then the patient's condition should be analysed, and other treatment options should be considered. In case of an adequate response to mannitol, osmotherapy can be continued as a continuous infusion of mannitol at a dose of 50-200 mg per day. The goal should be to establish urine output at a level of at least 30-50 ml per hour. Mannitol is used for the prevention and initial treatment of acute renal failure in haemolytic syndromes, rhabdomyolysis, the introduction of iodine-containing X-ray contrast agents, as well as in the early period after cadaveric kidney transplantation. In the 1980s, mannitol was used quite often in hepatobiliary surgery, especially in the presence of hyperbilirubinemia due to obstructive jaundice [7].

Mannitol is actively used as a nephroprotective agent during surgical treatment of abdominal aortic aneurysms. The use of mannitol not only avoids the development of acute renal failure in the postoperative period, but also significantly reduces the frequency and severity of subclinical kidney damage. Many authors also consider mannitol as a reliable means for preventing systemic disorders (in particular, pulmonary oedema), which often occur during operations for aneurysms of the abdominal aorta, as a result of reperfusion disorders after removal of the clamp from the aorta [8].

The antioxidant properties of mannitol made it possible to use it to prevent ischemic and post-reperfusion disorders during cardiac surgery – coronary artery bypass grafting, cor-

onary angioplasty, and surgical correction of heart defects. There are also reports of the use of mannitol as an antioxidant in the treatment of early myocardial infarction.

Promising is the use of mannitol in patients with compartment syndrome with limb injuries (subfascial oedema, local ischemia, neurological disorders) or crush syndrome. In both cases, the use of an osmodiuretic reduces the severity of local subfascial oedema, improves perfusion of the injured limb, and reduces the severity of post-reperfusion disorders [9].

Conclusion

Currently, the most commonly used osmotic diuretics include glycerol, mannitol, and urea. The principle of their action is aimed not only at causing forced diuresis, but also at ensuring the release of excess salts (primarily sodium ions), maintaining water-salt homeostasis and eliminating residues of nitrogen-containing compounds. At the same time, a decrease in blood viscosity and a decrease in renin secretion are achieved.

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