RISK OF OVERDOSE OF ANTIHYPERTENSIVE DRUGS

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Abstract: Adverse drug reactions are common and pose a serious health problem, limiting treatment options, causing compliance issues, and even leading to therapy discontinuation. Hypertension is a chronic disease that is regarded as a major risk factor for cardiovascular disease. To achieve a target blood pressure in an individual patient, a wide range of anti-hypertensive agents are available as single or combination therapy, whereas combination therapy increases the risk of developing Adverse Drug Reaction. Hypertensive patients frequently have coexisting disease conditions such as hyperlipidemia, impaired glucose metabolism, and renal impairment, which increase the risk of Cardio Vascular morbidity and mortality. When treating hypertensive patients, comprehensive management of both hypertension and concomitant Cardio Vascular Disease risk factors is essential. Some of the rare and serious Adverse Drug Reactions that occurred in patients treated with these drugs included beta-blockers causing psoriasis, calcium channel blockers causing gingival hyperplasia, peripheral oedema, Angiotensin Converting Enzyme inhibitors causing ankle oedema, and thiazide diuretics causing hyponatremia and hyperglycemia. Asymptomatic hypertension is more common and necessitates lifelong treatment with antihypertensive agents, predisposing to Adverse Drug Events. In order to improve treatment outcomes and reduce morbidity and mortality associated with adverse drug reactions, healthcare professionals must monitor adverse drug reactions in patients taking antihypertensive drugs.

Keywords: Adverse drug reactions, Hypertension, hyperlipidemia, glucose metabolism

Hypertension is one of the most common diseases of the cardiovascular system. According to WHO, every 3 adults in the world have high blood pressure (BP), that is, more than 30% of the adult population of developed countries have elevated blood pressure, and 15% have persistent arterial hypertension [1, 2]. To treat this disease, a wide arsenal (more than 500 brands) of drugs with different mechanisms of action is used, most of which are available without a prescription. Due to the widespread, often

uncontrolled use of antihypertensive drugs, an increase in acute poisoning with these drugs has been recorded in recent years [3]. Among them, the leading place is occupied by calcium channel blockers (CCBs); they are among the top five drugs, poisoning with which most often (36%) causes death [4]. Mortality is also common with the use of a2-adrenoceptor agonists. Severe poisoning with ACE inhibitors and antispasmodics is rare; they are more often observed when taken with other drugs [5]. Considering the danger of overdose of these groups of antihypertensive drugs, it is of interest to analyze, establish toxicodynamics and risk factors for intoxication. Symptoms of intoxication when taking CCBs occur in the first 1–4 hours, and in case of poisoning with long-acting drugs, signs of the toxic effect may not appear within 24 hours [4]. In the initial phase of CCB poisoning, the patient experiences imbalance, color perception (silver coloring of objects), drowsiness, nausea and vomiting. The reason for changes in color perception during CCB poisoning is a violation of blood flow in the retina of the eye [6]. The skin and mucous membranes become pale, dry, the pupils are dilated with no reaction to light, skeletal muscle tone and intestinal motility decrease sharply, and oliguria may occur [4]. In case of poisoning with a drug from the CCB group verapamil, the sinus rhythm slows down, pronounced bradycardia occurs, the contractile function of the heart weakens, which is manifested by a decrease in cardiac output and diuresis, and "early" collapse and intoxication psychosis develop. The development of intoxication psychoses with an overdose of CCB is associated with a violation of the synthesis and release of CNS mediators, as well as with a change in the activity of the enzyme involved in the synthesis of dopamine - dopamine-b-hydroxylase.

Hyperglycemia caused by CCB intoxication results from decreased insulin secretion (due to blockade of calcium channels in pancreatic b-cells), as well as increased release of endogenous catecholamines with subsequent increased gluconeogenesis in the liver and decreased glucose utilization. The cause of angina attacks is the development of a typical "steal phenomenon," and disturbances in intrarenal hemodynamics are a consequence of an imbalance between endogenous vasoconstrictors (renin) and vasodilators (prostaglandin E2), caused by CCBs and leading to the development of oliguria. There are 3 degrees of BCC poisoning. Mild degree: sinus bradycardia (up to 60 beats/min), moderate hypotension (up to 100 mm Hg), the patient's condition is stable, consciousness is clear. Moderate degree: hypotension (from 80 mm Hg and below), severe sinus bradycardia, arrhythmia and other cardiac disorders that lead to deterioration of systemic hemodynamics. Severe degree: terminal hemodynamic disorders, complete atrioventricular block, impaired cerebral blood flow. Cardiac and hemodynamic symptoms of BCC intoxication are associated with an obstacle to the entry of Ca2+ through "slow" L type channels, which are localized in the structures of the heart, the smooth muscles of the arteries, and in

much smaller quantities in the smooth muscles of the bronchi, intestines, uterus and in platelets. The toxic effects of CCBs are more pronounced with increasing ambient temperature. High sensitivity to BCC – among newborns and children under 1 year of age. Patients with diseases of the cardiovascular system are also at risk. Patients with the obstructive form of hypertrophic cardiomyopathy are especially predisposed to the development of life-threatening hemodynamic disorders, in which a decrease in systemic pressure increases obstruction both by a reflex (due to sympathetic stimulation in the early period of intoxication) and by reducing the postload (throughout the toxicogenic phase poisoning). Also diseases representing a risk group are sick sinus syndrome, atrioventricular conduction disorder, and pulmonary hypertension. Poisoning is facilitated by the simultaneous use of CCBs with b-blockers, cardiac glycosides, nitrates, diuretics, disopyramide, quinidine, lithium salts, ethanol. All CCBs bind to blood proteins, so if they are prescribed with quinidine, cardiac glycosides, or anticoagulants that can displace them from complexes with proteins, the concentration of calcium antagonists may increase. Verapamil, nifedipine, which have a high affinity for protein and displace any drug from its connection with it, can enhance the toxic effect, sharply increasing its content in the blood in a free state. Diltiazem should be prescribed with caution to elderly people with liver and kidney diseases. The combination of drugs from the CCB groups (especially verapamil, gallopamil, diltiazem) contributes to the occurrence of bradycardia, conduction disturbances, and heart failure.

All CCBs undergo biotransformation in the liver, and deterioration of its function (for example, due to hypoxia) slows down their elimination from the body. In case of an overdose of verapamil, when blood flow in the liver and the supply of oxygen to it deteriorates, the metabolism of verapamil is disrupted, and its half-life can increase several times. Verapamil is converted to norverapamil, which has a longer lasting cardiotoxic effect. Only 5% of the administered dose of verapamil is excreted unchanged. The combination of a CCB with procainamide, quinidine, disopyramide, and amiodarone enhances the cardiotoxic effect; combination with muscle relaxants leads to hypotension, cardiodepression, and cardiac arrhythmias; combination with glucocorticoids, diuretics, amphotericin B – leads to heart rhythm disturbances and hypokalemia. The main symptoms of poisoning by peripheral vasodilators are: hypotension, reflex tachycardia, metabolic acidosis, impaired consciousness, hyperglycemia, hyperthermia, "lupus syndrome," allergic reactions (swelling of the joints, erythematous skin rashes), anemia, leukopenia, paresthesia, polyneuritis, headache, dizziness, collapse. An overdose of diazoxide may cause hypocalcemia, hyperglycemia, cardiac arrest, and respiratory depression. Headache, dizziness, loss of consciousness are associated with the fact that when taking large doses of peripheral

vasodilators, blood redistribution occurs: due to a pronounced decrease in the tone of the blood vessels of the systemic circulation, blood flow in the internal organs (kidneys, lungs, heart) increases and at the same time intracranial pressure decreases, which leads to short-term loss of consciousness and collapse. Pulsating headaches are also associated with vasodilation due to the release of histamine (hydralazine hydrochloride inhibits the enzyme histaminase). The autoimmune reaction "lupus syndrome" is the most serious complication that occurs with long-term (more than 6 months) use of hydralazine hydrochloride. It is similar to systemic lupus erythematosus and rheumatoid arthritis and is caused by a violation of cellular immunity and the formation of IgG-containing complexes (antinuclear antibodies). Observed at doses above 200 mg/day, it is especially characteristic of "slow acetylators" of hydralazine with the presence of HLA-DRH antigens. The phenomena of late intoxication (anemia, leukopenia, paresthesia and polyneuritis) develop due to a deficiency of vitamin B6 due to the increased release of the coenzyme pyridoxal-5-phosphate from the body. The toxicity of sodium nitroprusside is associated with the formation of free cyanide during its metabolism, the concentration of which above 120 mg/l in blood plasma is considered toxic. Cyanide in liver mitochondria is quickly transformed by the enzyme rhodanose into thiocyanate. Concentrations of cyanide and thiocyanate should not exceed 500 μg/l and 100 mg/l respectively. Thiocyanate is mainly excreted by the kidneys.

Poisoning with peripheral vasodilators (hydralazine hydrochloride, diazoxide, minoxidil, sodium nitroprusside) most often occurs during overdose due to prehospital bolus administration or prolonged infusion administration, in which the dose of sodium nitroprusside exceeds 10-15 mcg/kg/hour. "Lupus syndrome" requires immediate withdrawal of hydralazine hydrochloride and administration of glucocorticoids. Due to the risk of accumulation of hydralazine hydrochloride, patients with impaired liver and kidney function should take hydralazine hydrochloride at intervals of 16 hours. Many years of experience in the use of antihypertensive drugs have identified factors that increase their toxicity. Thus, the use of diazoxide in combination with hydralazine is potentially dangerous due to the likelihood of a sharp drop in blood pressure. It should not be combined with diuretics, as they cause more severe hyperuricemia and hyperglycemia. In patients with epilepsy and taking phenytoin, seizures may reappear when using diazoxide. Intoxication with sodium nitroprusside occurs more often in patients with insufficient renal function and malnutrition. An overdose of ACE inhibitors (ACEIs) causes angioedema, oropharyngeal edema involving the tongue, and swelling of other areas of the body. Hypotension, bradycardia, electrolyte imbalance, hyperkalemia, renal failure, and shock are also observed. Blocking the renin-angiotensin system by ACE inhibitors in these patients provokes a sharp decrease

in glomerular pressure, intensity and filtration rate, and this contributes to the development of renal failure. It is also possible to develop nephrotic syndrome caused by membranous glomerulonephritis. ACE inhibitors should be prescribed with caution to patients with renovascular hypertension, as they may cause deterioration of renal function, particularly in persons with unilateral renal artery stenosis. This is explained by the fact that the perfusion pressure in the pathological kidney depends on the action of locally produced angiotensin. ACEIs, diuretics and other antihypertensive drugs in combination with alcohol intake create a risk of orthostatic collapse. Caution must be exercised when prescribing ACE inhibitors to patients with severe water-electrolyte imbalances, chronic heart failure, autoimmune diseases and collagenoses, cerebrovascular diseases (including cerebrovascular insufficiency, coronary artery disease), diabetes mellitus, hyperkalemia, with simultaneous administration glucocorticosteroids, cytostatics and antimetabolites. The combination of ACE inhibitors with potassium-sparing diuretics leads to an increase in potassium levels in the blood - hyperkalemia, and with loop and thiazide diuretics, beta-blockers and other antihypertensive drugs, neuroleptics (phenothiazines), nitrates, it enhances the hypotensive effect, and collapse is possible. Impaired renal function up to the development of renal failure due to ACEI intoxication occurs in patients with significant water-sodium losses (strict salt-free regimen, taking diuretics), or in patients with renal artery stenosis.

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