ANTIHYPERTENSIVE DRUG WITHDRAWAL SYNDROME

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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: Withdrawal Syndrome, Hypertension, hyperlipidemia,

An increase in the concentration of urea and creatinine in the blood serum is associated with patients taking diuretics (in parallel with ACE inhibitors); nephrotic syndrome develops against the background of proteinuria. Treatment with ACE inhibitors should be started with low doses. To prevent a sharp decrease in blood pressure in patients with low levels of sodium chloride and fluid in the body (vomiting, diarrhea, taking diuretics), before starting treatment, disturbances in water and electrolyte metabolism should be corrected by increasing the volume of circulating blood. Overdose of myotropic antispasmodics is rare. The most common overdose of bendazole is observed, which is manifested by collaptoid reactions and tachycardia.

From the central nervous system, dizziness and loss of consciousness are observed. The mechanism of toxic action of spasmolytics is associated with the effect of the drugs on the activity of the phosphodiesterase enzyme and the accumulation of cAMP. The adrenergic agonist clonidine (imidazoline derivative) is one of the representatives of the group of antihypertensive neurotropic drugs and causes severe poisoning. Victims complain of deterioration in general condition, weakness, lethargy, and dizziness. CNS depression gradually increases from drowsiness and stupor to the development of coma in severe poisoning with the development of respiratory and cardiovascular failure: orthostatic collapse, bradycardia, sinoatrial block, "escaping" rhythms, AV block. Signs of "sympatholytic" syndrome develop and increase (decrease in blood pressure, bradycardia, dullness of heart sounds, increased skin moisture is replaced by dry skin and mucous membranes, hypothermia, pale and cold skin, miosis, decreased peristalsis - constipation). Mydriasis is possible in cases of severe clonidine poisoning or progression of the severity of poisoning (increasing hypoxia). Hypoglycemia (in children), transient hyperkalemia and hypernatremia are also observed. A sign of the severity of clonidine poisoning is hypoxia without hypercapnia. The degree of blood pressure reduction correlates with the increase in hypoxia. The mechanism of the toxic effect of clonidine is associated with the effect on the α2-adrenergic receptors of the neurons of the vasomotor center, which causes their hyperpolarization, and on the presynaptic α2-adrenergic receptors of the endings of the adrenergic neurons of the medulla oblongata (in particular, the locus coeruleus). In this case, the release of norepinephrine eliminates the activating effect of the locus coeruleus on the vasomotor center. At the same time, clonidine inhibits the release of norepinephrine from the adrenal medulla and from adrenergic terminals (implementation of a negative feedback mechanism due to stimulation of central presynaptic α2-adrenergic receptors), which is accompanied by a decrease in the concentration of catecholamines in the blood. Clonidine, when interacting with fluoro rotane, enflurane, pentothal, and pan curonium, leads to severe hypotension.

When clonidine is administered simultaneously with reserpine, drowsiness and depression increase, and with quinidine - bradycardia. Combined poisoning with clonidine and other depressant substances (alcohol, neuroleptics, tranquilizers) is severe due to deep depression of the central nervous system. Potentiation of hypotensive effects determines the severity of clonidine poisoning in combination with diuretics and vasodilators. The combination of clonidine, cardiac glycosides, beta-blockers is dangerous due to bradycardia and the development of AV blockade. Clonidine poisoning is unfavorable for children with underlying cardiac rhythm and conduction disorders. The neurotoxicity of b-blockers is manifested by stupor, dizziness, coma, convulsions, drowsiness, symptoms of parkinsonism (reserpine), delirium. Cardiovasotoxic effects of beta-blockers: arrhythmia, sinus bradycardia,

arterial hypotension, cardiac conduction disturbances, cardiogenic shock. Poisoning with b-blockers contributes to bronchospasm, the development of hypoxia and metabolic disorders (hypoglycemia, hypokalemia). The toxic effect on the gastrointestinal tract is manifested by nausea, vomiting, diarrhea with preserved peristalsis. Poisoning with adrenoblockers is characterized by weakness and increased moisture of the skin, hypothermia (especially under the influence of b-blockers), as well as redness and itching (to a greater extent under the influence of a-blockers). a- and b-adrenergic blockers, when combined with MAO inhibitors, can cause stroke, cerebral edema, cardiac arrhythmias, and hypertensive crisis. a-blockers when used simultaneously with b-blockers, calcium antagonists, and diuretics lead to the risk of a sharp drop in blood pressure. In patients with diabetes mellitus, beta-blockers intensify and prolong hypoglycemia caused by insulin. When combining sugar-lowering drugs and beta-blockers, there is a possible risk of hypoglycemic coma. b-Adrenergic blockers in combination with antiarrhythmic drugs lead to cardiac arrhythmias and collapse, and their combination with cardiac glycosides results in severe bradycardia. The interaction of b-blockers with clonidine leads to a sharp decrease in blood pressure and bradycardia. Antihistamines and neuroleptics in combination with beta-blockers lead to ventricular arrhythmias. Propranolol and prazosin have a high affinity for protein, displacing any drug from its connection, and can enhance its toxic effect. The simultaneous use of bisoprolol and iodine-containing drugs increases the risk of developing anaphylaxis. Co-administration of bisoprolol, carvedilol and antiarrhythmic drugs increases the risk of developing heart failure. Lipid-soluble beta-blockers quickly penetrate organs and tissues, including the central nervous system, so when they are poisoned, neurotoxic effects often occur. Propranolol and oxprenolol bind best to plasma proteins (90%), atenolol and sotalol bind to them to a lesser extent (8%).

These features must be taken into account when using extracorporeal detoxification methods (hemodialysis, hemosorption, etc.) in the treatment of poisoning, since the stronger the bond with proteins, the less effective a number of detoxification therapy methods are. Reserpine disrupts the transport of catholamines (dopamine, norepinephrine and serotonin) in the presynaptic endings of sympathetic nerves due to the compaction of their membranes and a decrease in the activity of translocase, which transfers dopamine into vesicles. Disruption of the processes of transport and deposition of dopamine in the neurons of the central nervous system is accompanied by the appearance of symptoms of parkinsonism. The first signs of reser pin poisoning may appear after 5–7 hours: excitement, euphoria. While consciousness is preserved, children complain of a feeling of nasal congestion, difficulty breathing through the nose, and abdominal pain. Clinically, a nasal voice, swelling of the face,

and signs of cholinergic syndrome (bradycardia, decreased blood pressure, miosis, hyperhidrosis, increased intestinal motility) are detected. The skin is moist, hyperemic, warm to the touch, body temperature is elevated, the sclera is injected. Dyspeptic symptoms (abdominal pain, vomiting, diarrhea) occur as a result of a combination of cholinergic effects (increased peristalsis) and the simultaneous release of histamine and gastrin by the cells of the gastric mucosa. Children poisoned with reserpine are drowsy and adynamic. There is a shaky gait, tremor of the fingers and other phenomena of parkinsonism. Central nervous system depression increases, stupor is replaced by doubtfulness, preserved or increased spinal reflexes. Subsequently, coma develops, accompanied by clonicotonic convulsions. The condition is aggravated by the development of orthostatic collapse. Reserpine enhances the effects of central nervous system depressants, beta-blockers, and antihypertensive drugs; increases the incidence of adverse reactions of cardiac glycosides. The simultaneous administration of reserpine and MAO inhibitors can cause a more pronounced drop in blood pressure than when taking each drug separately. Sometimes toxic doses of reserpine cause the development of severe agitation, hallucinations and coma are possible. Reserpine lowers blood pressure, inhibits heart function, and narrows the coronary arteries (possible chest pain). There is a violation of the rheological properties of sputum, which is accompanied by the development of pneumonia. In case of poisoning, reserpine increases the secretion of antidiuretic hormone. This is accompanied by fluid retention and an increase in Na+ concentration in the body. In conditions of the development of cholinergic syndrome (with bradycardia), there is a high risk of pulmonary edema. Thus, analysis of toxicodynamics, the mechanism of development of intoxication and factors contributing to poisoning with antihypertensive drugs are the etiopathogenetic basis for the diagnosis of poisoning and measures to prevent these conditions. In case of an overdose of antihypertensive drugs, the main symptoms are collapse, bradycardia, loss of consciousness, drowsiness (with the exception of reserpine), hypoxia, renal failure (CCBs, peripheral vasodilators, ACE inhibitors), hyperglycemia (CCBs, peripheral vasodilators, clonidine, b- adrenoblockers), bradycardia (CCBs, ACE inhibitors, clonidine, b-blockers, reserpin), tachycardia, loss of consciousness (peripheral vasodilators, spasmolytics), drowsiness, nausea, vomiting (CCBs, b-blockers).

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