MODERN METHODS OF TREATMENT OF PATIENTS WITH HYPERTENSIVE CRISIS

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Summary. The article is devoted to the discussion of modern approaches to diagnosis and treatment in complicated and uncomplicated hypertensive crisis. The options for the choice of antihypertensive drugs are considered, depending on the nature of target organ damage in hypertensive crisis. The data on the most frequently prescribed drugs for complicated and uncomplicated hypertensive crisis are presented.

Introduction

Uncontrolled arterial hypertension (AH) is a serious clinical problem that directly determines the immediate and long-term prognosis of the patient (Andersen UO, 2017). The results of observational, clinical and prospective studies have shown that adequate control of hypertension in routine clinical practice is the exception rather than the rule (Go AS et al., 2014; Janke AT et al., 2016). Only 10-15% of all hypertensive patients reach the target blood pressure (BP) level and are able to maintain it at this level for a long time (National Heart, Lung, and Blood Institute, 2003; CDC, 2011). Within 3 years, about 30% of all patients with uncontrolled hypertension die from cerebral stroke, end-stage renal dysfunction or heart failure (Hoekstra J., Qureshi A., 2008; Heath I., 2016).

Despite the fact that there is no single definition of a hypertensive crisis, most experts from various medical associations (James PA et al., 2014) agree that a hypertensive crisis can be defined as a condition with a pronounced increase in blood pressure (> 180/110 mm Hg. .), which is accompanied by the appearance or aggravation of clinical symptoms associated with damage to target organs, and requires a rapid controlled decrease in blood pressure (Chobanian AV et al., 2003).

The working group on hypertension of the Ukrainian Society of Cardiology defines a hypertensive crisis as a sudden significant increase in blood pressure from a normal or elevated level, which is almost always accompanied by the appearance or intensification of disorders on the part of target organs or the autonomic nervous system (Parkhomenko A.N. et al., 2013) .

It should be noted that no direct relationship has been established between the severity of target organ damage and the absolute value of blood pressure, although a sharp increase in blood pressure from the normotensive level to 170 mm Hg. Art. and higher (for example, with eclampsia) is often accompanied by the development of a life-threatening situation (Gegenhuber A., Lenz K., 2003).

Alcohol or smoking abuse (Gegenhuber A., Lenz K., 2003). Factors that worsen the prognosis in hypertensive crisis include a long duration of hypertension, elderly and senile age, an increase in the level of creatinine and urea in the blood> 220 μmol / L and> 10 mmol / L, the presence of severe hypertensive retinopathy (extravasal exudation and hemorrhages) (Varon J., Marik PE, 2000; Vaughan CJ, Delanty N., 2000).

Thus, all cases of a sharp increase in blood pressure can be divided into states without an immediate threat to life (uncomplicated crisis) and life-threatening (complicated crisis) (Phan DG et al., 2015). In fact, most of the recommendations categorize only the last type of conditions in the category of "hypertensive crisis", defining cases with no immediate threat to the patient's life as hypertension, treated inadequately (Shafi T., 2004; Mancia G. et al., 2013). Nevertheless, from a practical point of view, the division of hypertensive crises into complicated (hypertensive emergency) and uncomplicated (hypertensive urgency) is quite rational, since it largely determines the doctor's tactics in relation to the magnitude and rate of decrease in blood pressure, determining the routes of drug administration,

Principles of hypertensive crisis treatment

Treatment of emergency conditions in hypertension depends on the initial value of blood pressure, the presence and type of target organ damage, concomitant diseases and often ranges from expectant tactics to an aggressive controlled decrease in blood pressure to the target (Vaughan CJ, Delanty N., 2000). In most cases, in uncomplicated hypertensive crisis, it is recommended to provide a quick, but incomplete, decrease in blood pressure by at least 25% of the initial one within 24-48 hours, followed by dose adjustment of antihypertensive drugs for subsequent maintenance therapy (Berezin A.E., 2013a; b). Medicines can be administered orally or sublingually, and hospitalization is usually not required (Berezin O.Y., 2016).

In complicated hypertensive crisis, parenteral administration of drugs with a proven dose-dependent effect on blood pressure is necessary (Aggarwal M., Khan IA, 2006). The rate of controlled decrease in blood pressure in a complicated hypertensive crisis is usually 15–25% of the initial value within 1–2 hours, then within 2–6 hours the blood pressure level should reach 160–150 / 100–90 mm Hg. Art. (Mancia G. et al., 2013; Weber MA et al., 2014). Subsequently, supportive treatment is required with oral antihypertensive drugs (Berezin A.E., 2009). In all these situations, hospitalization of the patient is usually required for urgent

indications (Weber MA et al., 2014). However, these general principles are not applicable to all situations considered as complicated hypertensive crisis (Table 1).¬

Table 1. Rate of decrease and target blood pressure levels in patients with various complicated hypertensive crises

Comorbid state	Rate of BP decrease	Target level
Acute hypertensive encephalopathy	Reduction of mean blood pressure by 25% within 8 hours	Installed individually. An acceptable level of systolic blood pressure may be <160 mmHg. Art.
Ischemic cerebral stroke	It is set individually if blood pressure is> 220/120 mm Hg. Art.	Not determined. For patients undergoing thrombolytic therapy, systolic blood pressure is <185 mm Hg. Art.
Hemorrhagic stroke	It is set individually if blood pressure is> 220/120 mm Hg. Art.	During the first 24 hours after the onset of symptoms, with increased intracranial pressure, an average blood pressure of <130 mm Hg is maintained. Art. (systolic blood pressure <180 mm Hg), in patients without increased intracranial pressure, the mean blood pressure is maintained within <110 mm Hg. Art. (systolic blood pressure <160 mm Hg)
Subarachnoid hemorrhage	Decrease in blood pressure to the target level within 1 hour	Systolic blood pressure <140 mm Hg. Art. while maintaining intracranial angiospasm
Acute coronary syndrome / myocardial infarction	Decrease in mean blood pressure by 20–30% of baseline within 1 hour. Relative contraindication for thrombolytic therapy is blood pressure> 185/100 mm Hg. Art.	<140/90 mm Hg Art.
Acute heart failure / pulmonary edema	Decrease in blood pressure to the target level within 1 hour	<140/90 mm Hg Art.
Aortic dissecting aneurysm	Decrease in mean blood pressure by 25% of the baseline during the first 5-10 minutes, and then - within 20-30 minutes to the target level	Systolic blood pressure 110–100 mm Hg. Art.
Eclampsia	Reduction of mean blood pressure by 20% of baseline within 12-24 hours	Not determined

With dissecting aortic aneurysm, a rapid decrease in mean blood pressure by 25% of the initial one is required during the first 5–10 minutes, and then within 2 hours the target systolic blood pressure, corresponding to 110–100 mm Hg, must be achieved. Art. (Gegenhuber A., Lenz K., 2003). In acute disorders of cerebral

circulation, including cerebral infarction, the rate of decrease in blood pressure should be slow and determined individually (Slama M., Modeliar SS, 2006). In this case, antihypertensive therapy is not carried out with systolic blood pressure <220 mm Hg. Art. and / or diastolic blood pressure <120 mm Hg. Art. The exception is patients undergoing thrombolytic therapy, for whom the target systolic blood pressure should be <185 mm Hg. Art. (James PA et al., 2014). In acute hypertensive encephalopathy, an immediate decrease in mean blood pressure by 20% of baseline is required within 1 hour of medical care to achieve a target diastolic blood pressure <110 mm Hg. Art.

In general, recommendations for the treatment of hypertensive crises are based on expert opinion, since randomized clinical trials in this direction with a sufficiently high statistical power have not been carried out (British Columbia Ministry of Health, 2014).

Features of drug therapy in patients with complicated and uncomplicated hypertensive crisis

For uncomplicated hypertensive crisis, antihypertensive drugs are recommended (captopril, nifedipine, including in the form of slow release GITS, labetalol, urapidil), which provide a relatively gradual decrease in blood pressure within 24 hours, and can also be prescribed sublingually, which makes it possible to obtain an antihypertensive effect already in the first 10–20 minutes without a significant risk of hypoperfusion of target organs.

Captopril - the first fully synthetic angiotensin-converting enzyme (ACE) inhibitor - has a vasodilating effect, reducing afterload, pulmonary capillary wedge pressure and pulmonary vascular pressure; increases exercise tolerance; has reno- and cardioprotective, anti-ischemic and weak diuretic effects (Slama M., Modeliar SS, 2006). Captopril is able to reduce the mass of the left ventricular myocardium, prevent the onset and progression of heart failure. When taken sublingually at a dose of 12.5-25 mg, blood pressure decreases after 15-30 minutes and remains within 6-8 hours. The most common side effects are dry or unproductive persistent cough, tachycardia, headache, hypotension in orthostasis, skin itching , hyperkalemia, neutropenia. The drug is contraindicated in pregnant women,¬

Nifedipine GITS - a dihydropyridine derivative of calcium channel blockers, has a vasodilating effect, a moderate negative chronotropic effect, increases the volumetric velocity of coronary and cerebral blood flow, and reduces the pressure in the pulmonary artery system. It is usually used to relieve mild uncomplicated hypertensive crisis, but a wide range of side effects, including reflex tachycardia, periorbital and peripheral edema, skin redness, pruritus, limits its use (Phan DG et al., 2015).

Clonidine is a fairly old and well-studied drug related to peripheral α-adrenergic receptor blockers with central α-agonistic and peripheral anticholinergic effects (Slama M., Modeliar SS, 2006). The drug has lost its significance as the main drug for the relief of hypertensive crisis, although the current clinical guidelines provide for this possibility (Phan DG et al., 2015).

In a complicated hypertensive crisis, drugs administered parenterally must satisfy the main condition for the provision of emergency medical care, namely, to provide a dose-dependent controlled decrease in blood pressure (Feldstein C., 2007; Ardigo S. et al., 2008). With the ineffectiveness of monotherapy, various combinations of drugs are possible (Berezin O.Y., 2016).

Sodium nitroprusside is a powerful venous and arterial vasodilator with a fast-onset effect (within a few seconds), which is the first-line drug for most urgent clinical situations associated with the development of complications of uncontrolled hypertension (Murphy C., 1995). Its administration is carried out by titration with an individual dose selection, which requires constant monitoring of blood pressure (ideally, direct invasive measurement). The main indications for the appointment of sodium nitroprusside are acute hypertensive encephalopathy, acute or acutely decompensated heart failure, dissecting aortic aneurysm, hyperadrenergic conditions (Pergolini MS, 2009). Since the main metabolite of the drug is thiocyanate, the duration of continuous intravenous infusion can be preventively limited to 48-72 hours, especially in patients with renal and hepatic impairment. Thiocyanate intoxication is manifested by nausea, vomiting, muscle cramps, decreased superficial and tendon reflexes, disorientation, and sometimes psychosis. In these cases, sodium thiosulfate is recommended as an emergency. Sodium nitroprusside in high doses is able to increase intracranial pressure, which limits its use in patients with cerebrovascular diseases, traumatic brain injury, after cranial operations (Phan DG et al., 2015). It must be borne in mind that the drug has a pronounced irritant effect when it gets under the skin and sometimes causes subcutaneous necrosis. decreased superficial and tendon reflexes, disorientation, sometimes psychoses. In these cases, sodium thiosulfate is recommended as an emergency. Sodium nitroprusside in high doses is able to increase intracranial pressure, which limits its use in patients with cerebrovascular diseases, traumatic brain injury, after cranial operations (Phan DG et al., 2015). It must be borne in mind that the drug has a pronounced irritant effect when it gets under the skin and sometimes causes subcutaneous necrosis. decreased superficial and tendon reflexes, disorientation, sometimes psychoses. In these cases, sodium thiosulfate is recommended as an emergency. Sodium nitroprusside in high doses is able to increase intracranial pressure, which limits its use in patients with cerebrovascular diseases, traumatic brain injury, after cranial operations (Phan DG et al., 2015). It must be borne in mind that the drug has a pronounced irritant effect when it gets under the skin and

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Nitroglycerin is a powerful peripheral, predominantly venous (in low doses) vasodilator that reduces pre- and afterload, increases volumetric coronary blood flow and perfusion (Wilson SS et al., 2017). Nitroglycerine, apparently, is the best drug for the relief of hypertensive crisis complicated by acute coronary syndrome, myocardial infarction, pulmonary edema or acute heart failure (Berezin A., 2015; Wilson SS et al., 2017). In addition, it is most often used to achieve adequate blood pressure control in patients with hypertensive crises in the postoperative period after coronary artery bypass grafting or other cardiac / vascular surgery, including angioplasty for dissecting aortic aneurysms (Sun SH et al., 2016). Tolerance to nitroglycerin begins to develop after 24–48 hours of continuous slow infusion, which may have serious clinical significance (Phan DG et al., 2015). The drug is contraindicated in many cerebrovascular diseases,

Nicardipine is a dihydropyridine slow calcium channel blocker with a relatively rapidly emerging antihypertensive effect of moderate duration (Dahlöf B., 2009). Most often, nicardipine is used in patients with cerebrovascular diseases or in persons with hypertensive crises during the perioperative period. A drug interaction has been described between nicardipine and some inhaled anesthetics (Elliott WJ, 2004). Among the most common side effects are headache, dizziness, periorbital and peripheral edema, skin redness and itching, which are characteristic of many representatives of this class of drugs (Berezin A.E., 2015).

Nimodipine is a typical representative of short-acting dihydropyridine derivatives of slow calcium channels. The drug is reserved for the relief of hypertensive crises accompanied by subarachnoid hemorrhage and intracranial angiospasm (Etminan N., Macdonald RL, 2017; Hockel K. et al., 2017). There are at least two randomized clinical trials (Pickard JD et al., 1989; Hänggi D. et al., 2015) and a meta-analysis by N. Etminan et al. (2011) that demonstrated a beneficial effect of long-term nimodipine infusion on survival and the risk of repeated intracranial hemorrhage. (Kumar A., Phalak M., 2017).¬¬

Fenoldopam is a selective agonist of dopaminergic receptors of the first subtype, which are responsible for arteriolar vasodilation, natriuresis and diuresis (Murphy MB et al., 2001). These qualities of the drug are most in demand in patients with hypertensive crisis complicated by acute kidney injury. Fenoldopam has a rapid antihypertensive effect, does not require invasive blood pressure monitoring, does

not require dose titration and does not cause withdrawal syndrome (Feldstein C., 2007). In terms of effectiveness, fenoldopam and sodium nitroprusside are very close, however, the ease of administration of fenoldopam is its indisputable advantage. The main candidates for treatment with fenoldopam are patients with hypertensive crisis complicated by acute renal injury, or persons with previously verified chronic kidney disease (Murphy C., 1995).¬

Labetalol is a non-selective β- and α-blockerone-adrenergic receptors (in a ratio of 3-7: 1), characterized by the rapid development of a therapeutic effect that lasts for 2-12 hours, and low toxicity (Feldstein C., 2007). The drug reduces peripheral vascular resistance without reactive sympathetic stimulation and does not require intravascular monitoring of blood pressure (Henny-Fullin K. et al., 2015). The use of labetalol in hypertensive crises is most justified in cases of the development of acute hypertensive encephalopathy, stroke, hyperadrenal conditions (Henry CS et al., 2004). In this case, the drug is contraindicated in acute heart failure, high-grade intracardiac blockade, bronchial asthma and chronic obstructive pulmonary disease.

Esmolol is an ultra-short, highly selective β blockerone-adrenergic receptors without intrinsic sympathomimetic activity, which is approved by the Food and Drug Administration (FDA) exclusively for the relief of perioperative hypertensive crisis, since its use requires intra-arterial blood pressure monitoring. Theoretically, if intra-arterial blood pressure monitoring is provided, then the drug can be prescribed for acute coronary syndrome / myocardial infarction, acute hypertensive encephalopathy, pheochromocytoma, dissecting aortic aneurysm (Elliott WJ, 2004). It should be noted that esmolol often causes thrombophlebitis of peripheral veins, and its accidental ingestion under the skin leads to local necrosis of the subcutaneous tissue (Feldstein C., 2007). The drug cannot be used in patients

Phentolamine is a competitive non-selective blocker of α-adrenergic receptors, the use of which in hypertensive crisis is limited to a hyperadrenal state that develops as a result of drug interactions or pheochromocytoma (Dieterle T. et al., 2001). Intravenous bolus administration of the drug provides an immediate decrease in blood pressure by 5-10 mm Hg. Art. At the same time, the high risk of hypotension in orthostasis requires certain caution when using it (Feldstein C., 2007).

Hydralazine is a direct arteriolar vasodilator with the potential to improve placental blood flow (Duley L., 2003). This feature of the drug is the rationale for its use in eclampsia and preeclampsia, although the high frequency of unwanted side effects, including severe sympathetic stimulation, fluid retention, headache, skin redness, tachycardia, nausea and vomiting, significantly limit its clinical use (Henry CS et al. ., 2004). Moreover, the drug is prohibited for use in patients with high cardiovascular risk and persons with established cardiovascular disease (Henny-Fullin K. et al., 2015).

Urapidil - blocker αone-adrenergic receptors with the ability to stimulate serotonin 5-HT1A-receptors of the vasomotor center. The drug helps to reduce peripheral vascular resistance without reflex tachycardia and reduce cardiac output. A feature of urapidil is an extremely low frequency of hypotension in orthostasis, even in elderly and senile patients (Yang W. et al., 2017). The main indication for the use of urapidil is the relief of a hypertensive crisis, especially associated with a hyperadrenal state, cerebrovascular diseases, eclampsia, dissecting aortic aneurysm (Wacker J. et al., 1999; Diemunsch P. et al., 2015). Contraindications to the use of urapidil are aortic stenosis, pregnancy and lactation, patent ductus arteriosus, hypersensitivity to the drug.

Enalaprilat is an injectable form of enalapril maleate recommended exclusively for controlled hypotension in order to relieve hypertensive crisis, mainly associated with the occurrence of acute hypertensive encephalopathy or heart failure (Ayaz SI et al., 2016; Lipari M. et al., 2016). The drug is administered at a dose of 1.25–5 mg intravenously bolus, the effect develops after 15 minutes and lasts up to 6 hours. Like ACE inhibitors, enalaprilat has class-specific contraindications that limit its use in pregnant women, patients with bilateral renal artery stenosis, severe renal dysfunction, hyperkalemia and angioedema.

Loop diuretics are often used to relieve various hypertensive crises. In fact, diuretics can be used in the treatment of refractory, malignant hypertension and uncomplicated hypertensive crisis. The main argument against the initial prescription of this class of drugs in complicated hypertensive crises is the absence of a predictable antihypertensive effect, and therefore they are not suitable for controlled hypotension (Dieterle T. et al., 2001). Current clinical guidelines do not recommend considering loop diuretics as the main component of the treatment of complicated hypertensive crisis (Mancia G. et al., 2013; Murphy C., 2015; Phan DG et al., 2015).

Kaptopres-Darnitsa is a combined antihypertensive drug containing a dosed combination of an ACE inhibitor captopril (50 mg) and hydrochlorothiazide (25 mg). Both active substances included in the fixed combination have a fairly solid evidence base in the treatment of hypertension (Souvirón Rodríguez A., Martínez Morillo M., 1992; Luccioni R. et al., 1995; Waeber B. et al. 1995). Kaptopres-Darnitsa has therapeutic bioequivalence in relation to the original reference drug and is recommended for initial therapy and maintenance treatment in mild and moderate hypertension in order to achieve optimal blood pressure control, reduce the risk of cardiovascular events, including hypertensive crises, improve the quality and duration of life, and can also be used in the relief of uncomplicated hypertensive crises, including as a component of responsible self-medication (Ferroni C. et al., 1992; Klein G., 1998). The initial dose of the drug may be ½ tablet (25 mg of captopril and 12.5 mg of hydrochlorothiazide) once a day. The therapeutic effect

appears after 30-60 minutes and lasts for 6-12 hours and sometimes more. In case of insufficient effectiveness, the dose can be doubled. For renal dysfunction (glomerular filtration rate> 30 ml / min / 1.73 m¬¬2) it is recommended to reduce the dose of the drug by half. With severe renal failure, during pregnancy, with bilateral renal artery stenosis, angioedema in the anamnesis, Kaptopres-Darnitsa is not used.

In general, the drug has a good efficacy profile, an acceptable safety spectrum and a fairly democratic cost, which makes it one of the most affordable drugs for the initial treatment of mild / moderate hypertension. Kaptopres-Darnitsa can be recommended for the relief of uncomplicated hypertensive crisis, including situations involving responsible self-medication, as well as as the main drug in monotherapy or in combination for initial therapy and long-term maintenance treatment of hypertension.

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