

Approaches To The Tactics Of Treatment Of Pulmonary Hypertension

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Abstract: A comparison of the causes of pulmonary hypertension. The article is devoted to a comprehensive study of pulmonary hypertension. Particular attention is paid to the treatment of pulmonary hypertension. The author concludes pulmonary hypertension is an urgent problem today. This problem has not been sufficiently studied and requires further research. The flock is generalized with new material on the topic under study.

Keywords: pulmonary hypertension, treatment strategy, classification, clinical picture.

Specific therapy.

Calcium antagonists.

The criteria for the potential effectiveness of calcium antagonist therapy in patients with PH are a positive pharmacological test with vasodilators (nitric oxide, prostaglandin E1): a decrease in SDL by more than 10 mm Hg. Art. to a level of less than 40 mm RT. Art. with an increase or constant value of cardiac output. Indications for the administration of calcium antagonists are a cardiac index of more than 2.1 l / min / m², saturation of venous blood with oxygen of more than 63%, pressure in the right atrium of less than 10 mm Hg. Art. The dose of drugs is selected, starting with the minimum, taking into account the level of DLA and

hemodynamic parameters. With right ventricular decompensation, amlodipine is the drug of choice.

Calcium antagonists are absolutely contraindicated:

- with a cardiac index of less than 2.1 l / min / m²;
- when saturated with blood oxygen in the pulmonary artery less than 63%;
- with a pressure in the right atrium of more than 10 mm RT. Art.

In patients with PH against the background of systemic diseases of the connective tissue, vasoreactivity tests often do not allow to establish the possible effectiveness of long-term therapy with calcium antagonists, and high doses of the latter are poorly tolerated. The beneficial effects of long-term therapy high-dose calcium antagonists are indicated in children with IPAH.

Prostaglandins.

Prostacyclin, produced mainly by endothelial cells, has a powerful vasodilating effect in all vascular pools, is a powerful endogenous inhibitor of platelet aggregation, and has cytoprotective and antiproliferative effects. The role of impaired prostacyclin production in patients with PH is proved as a decrease in the expression of prostacyclin synthase

in LA, and a decrease in the excretion of its metabolites in the urine. This is the basis for the use of prostacyclin for the treatment of patients with PH, although it has not yet been established whether a violation of the synthesis of prostacyclin is the cause or effect of PH.

In recent years, the use of prostacyclin in clinical practice has expanded due to the creation of its stable analogues with various pharmacokinetic features, but with qualitatively similar pharmacodynamic properties [5, 6]. Stable analogues of prostaglandin I₂ (prostacyclin) with a powerful vasodilating effect on the vessels of the pulmonary circulation are used abroad.

[7, 8]. In our country, a drug from this group is used - prostaglandin E1. The introduction of the drug begins with a dose of 5-10 ng / kg / min, which is gradually increased to 30 ng / kg / min by intravenous drip (courses of 2-3 weeks). Perhaps a combination with calcium antagonists. Prostaglandins E1 and I2 are indicated for PH III and IV FC (WHO), with a cardiac index of less than 2.1 l / min / m², oxygen saturation of venous blood

less than 63%, pressure in the right atrium more than 10 mm Hg In addition, prostaglandins can be prescribed before lung transplantation if conventional treatment is not effective. In randomized trials, the efficacy of epoprostenol (synthetic prostacyclin) in patients with PH on the background of systemic scleroderma, as well as in uncontrolled studies in children with IPAH, was shown [9].

Endothelin Receptor Antagonists (ARE). This class of drugs implements its action through the blockade of the action of endothelin-1 (ET-1) peptide of endothelial origin, characterized by powerful vasoconstrictor and mitogenic properties against smooth muscle cells due to binding to two types of receptors - type A, localized on smooth muscle cells and type B localized on endothelial and smooth muscle cells or exclusively type A receptors [10]. In our country is registered the drug of this group is a non-selective antagonist of endothelin receptors - bosentan. Bosentan is an oral antagonist of endothelin receptors that blocks both ETA and ETB receptors. Both types of receptors mediate the pathogenic effects of endothelin in various pathological conditions, such as PAH. In addition to reducing vasoconstriction, the drug inhibits fibrosis, inflammation, and vascular hypertrophy [11].

In children, the dose of bosentan is titrated depending on body weight. In an open, uncontrolled study in children with PAH aged 4–17 years (BREATHE-3), hemodynamic parameters improved by week 12 of treatment with bosentan as monotherapy or in combination with epoprostenol [12, 13].

An increase in transaminases is observed in approximately 10% of patients, reversible after a dose reduction or drug withdrawal. The most likely mechanism of action of bosentan on the level of liver enzymes is dose-dependent competition with bile salts, which leads to their delay, having a cytotoxic effect on hepatocytes [14,

fifteen]. Monthly monitoring of transaminase levels in the blood during treatment with bosentan is recommended.

Nitric oxide and phosphodiesterase type 5 inhibitors (IFDE-5). Nitric oxide is a powerful endogenous vasodilator that selectively acts on the vessels of the pulmonary circulation. 2-3-week courses of inhalation of nitric oxide of 20-40 ppm are prescribed for 5-6 hours a day. Sildenafil citrate is a potent selective type 5 phosphodiesterase inhibitor that prevents degradation of cyclic guanosine monophosphate (cGMP) and causes a decrease in pulmonary vascular resistance and overload of the right ventricle [16]. In uncontrolled clinical trials, sildenafil was used for IPAH, PH associated with SZST, congenital heart defects, LA thromboembolism and caused an improvement in hemodynamics and physical tolerance.

loads [17, 18, 19]. In a randomized trial SUPER-1 (Sildenafil Use in Pulmonary Arterial Hypertension) in 278 patients with PAH who received sildenafil citrate doses of 20, 40, 80 mg 3 times a day. Patients noted an improvement in clinical symptoms and an increase in exercise tolerance. The approved dose is 20 mg 3 times a day. However, a stable treatment effect was observed with a dose of 80 mg 3 times a day.

Promising treatment strategies.

Despite progress in the treatment of PAH patients, their functional status and survival remain unsatisfactory. Currently, the possibilities of influencing various pathophysiological mechanisms of the formation of the disease are being intensively studied in order to achieve maximum improvement of clinical

symptoms and prognosis. Phase II and III studies are conducted with the following drugs: NO-independent stimulators and activators of cGMP, inhaled vasoactive intestinal peptide, non-prostanoid prostacyclin receptor agonist, tissue specific double endothelin receptor antagonist, tyrosine kinase inhibitors, serotonin antagonists.

In experimental models, the strategy of gene therapy is being studied. On the monocrotaline model of LH in rats, the effectiveness of stem cell therapy has been shown [20].

Combination therapy.

It is known that the term “combination therapy” implies the simultaneous use of more than one class of specific drugs in the treatment of PAH patients, for example, ARE in combination with prostanoids or IFDE-5 or other new drugs.

In many specialized PAH treatment centers, combination therapy is the standard of treatment, however, the duration of this therapy, its effectiveness and safety have not been fully studied. A series of clinical studies have shown that various combinations are effective and safe. A relatively small study of BREATHE-2 revealed a tendency to improve hemodynamic parameters when prescribing combination therapy with epoprostenol and bosentan [12]. In the PACES study, sildenafil was added to intravenous epoprostenol therapy in 267 PAH patients. After 12 weeks of treatment, significant dynamics were observed in the 6-MX test, the time until the development of clinical deterioration. Cases of death of patients during the observation period were observed only in the placebo group. It is important to emphasize that the indication for combination therapy in PAH patients is the lack of stable

clinical effect. Due to the risk of systemic hypotension, special caution is required when using specific PAH therapy with antihypertensive drugs, such as β -blockers, angiotensin converting enzyme inhibitors, etc. [3].

Treatment of arrhythmias.

An important clinical problem in patients with PH is the treatment of arrhythmias. Compared with patients with left ventricular heart failure (HF), malignant rhythm disturbances, such as ventricular tachycardia, ventricular fibrillation, are more rare in PAH. Atrial flutter or atrial fibrillation occurs equally and lead to clinical deterioration and development of right ventricular heart failure phenomena. Treating atrial flutter is more effective than treating atrial fibrillation. Sinus rhythm restoration in patients with PH improves survival compared with patients with a constant form of atrial fibrillation, 80% of whom died within 2 years. However, there are no data from controlled trials or prospective observations that the goal of therapy should be to maintain a stable sinus rhythm. When choosing antiarrhythmic drugs, preference is given to those that do not have a negative inotropic effect, in particular, amiodarone. Atrial septostomy. The rationale for the atrial septostomy was observations that showed that the survival rate of patients with Eisenmenger syndrome and IPAH with an open oval window is better than in the case of an unchanged atrial septum. Creating a shunt from right to left allows you to reduce the average pressure in the right atrium and overload of the right ventricle, as well as increase the preload of the left ventricle and, thus, cardiac output [21]. Under the created conditions, transport O₂ improves, despite desaturation of arterial blood, decreases

sympathetic hyperactivation. The procedure is contraindicated with an average pressure in the right atrium > 20 mm Hg. Art., saturation O₂ <80% at rest. As a result of the intervention, there is a decrease in syncope, an increase in exercise tolerance. Atrial septostomy.

It is recommended only for patients with IV FC (previously also III FC) with frequent syncope and / or refractory right ventricular heart failure, despite ongoing drug therapy, including before transplantation.

Transplantation.

The use of specific therapy significantly reduced the need for transplantation. Unfortunately, approximately 25% of patients with IPAH do not show a significant improvement when prescribing specific therapy. The prognosis of patients with III-IV FC remains the edge is not unfavorable and depends on the etiology. So, in patients with PAH on the background of SZST it is worse than with IPAH. The best survival is observed in patients with PH with congenital heart defects, the worst prognosis is with pulmonary veno-occlusive disease, pulmonary capillary hemangiomatosis, when drug therapy is practically ineffective [22].

Patients with poorer prognosis should be included in the waiting list for heart-lung complex transplantation or bilateral lung transplantation. The exact statistics of complications in the form of the development of systolic dysfunction of the right ventricle and / or diastolic dysfunction of the left ventricle are unknown. According to the register of the International Society for Heart and Lung Transplantation, with Eisenmenger syndrome due to simple defects, the choice may be an isolated lung transplant with simultaneous correction of the disease. With ventricular defects, better outcomes are observed with transplantation of the heart-lung complex. Five-year survival in PAH patients averages 45-50%.

Evaluation of the effectiveness of treatment.

After 3-4 months from the start of drug therapy, it is necessary to assess the dynamics of the state of PAH patients - clinical symptoms, exercise tolerance (improved distance in the 6-MX test is more than 380 m), FC (WHO) - up to II. In case of negative dynamics of the functional status or absence of changes, transthoracic echocardiography and catheterization of the right heart are necessary. The question of combination specific therapy in patients with PAH should be discussed in determining the following parameters:

- heart index less than 2.4 l min / m²;

- pressure in the right atrium of more than 10 mm RT. st .;
- SDLA more than 30-40 mm RT. st .;
- decrease in total pulmonary vascular resistance

less than 30%.

Modern drug approaches using specific therapy drugs (endothelin receptor antagonists, type 5 phosphodiesterase inhibitors, prostaglandins) and their combinations open up new prospects for the effective treatment of PAH patients and improve their prognosis. In recent decades, in Uzbekistan there has been a steady increase in researchers' interest in the problem of assessing the function of the right and left ventricle of the heart, especially the diagnosis of its dysfunction (both systolic and diastolic) in chronic heart failure, LH and HPS. The course of LH and HLC, treatment and prophylactic programs largely depend on the timely management of effective management tactics. According to statistics, only 25% of cases of HLS are diagnosed in a timely manner. The reason for the increase in the prevalence and mortality from lung diseases and HLC in Uzbekistan is underdiagnosis and late detection. In order to establish early diagnosis, adequate prevention and treatment of LH and HLC, it is necessary to clarify the pathogenesis of the disease, factors leading to and aggravate their course.

At the same time, leading scientists agree that the mechanism of development of pancreatic remodeling in patients with lung diseases remains unclear. Criteria for predicting the development of pulmonary heart in patients with diseases of the lungs and / or hypoxia and premature mortality have not been developed. Further research is needed to answer these and other questions regarding the pathogenetic concept of cardiovascular remodeling in lung diseases. In studies of Uzbek scientists, it was proved that the LH and HLC syndrome has a significant effect

on the physical and mental state of patients, seriously violating the quality of their life. [23].

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