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ORAL ANTICOAGULANTS IN PATIENTS WITH DIFFERENT FORMS OF PULMONARY ARTERIAL HYPERTENSION, ASPECTS OF THE PROBLEM

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SUMMARY

The use of direct oral anticoagulants in patients with pulmonary arterial hypertension (PAH) has remained a controversial issue for a decade. Despite the lack of solid evidence from well-controlled prospective trials, anticoagulation has been recommended for patients with idiopathic pulmonary arterial hypertension (IPAH), but it is unclear whether this recommendation should be extrapolated to patients with other forms of PAH. In this review, we discuss the current opportunities and problematic aspects of oral anticoagulation therapy in different forms of PAH, the influence on disease course and prognosis..

Keywords: *pulmonary arterial hypertension, idiopathic pulmonary arterial hypertension, direct oralanticoagulants, thrombosis in situ.*

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Pulmonary arterial hypertension (PAH) is a condition, which is very often diagnosed at a late stage, with the functional class of pulmonary hypertension of III or IV level, according to the classification of the World health organization, and results in severe right heart failure and death. The diagnostic criteria for PAH include the level of mean pulmonary artery pressure ≥25 mmHg provided by right heart catheterization; pulmonary artery occlusion pressure ≤15 mmHg; pulmonary vascular resistance >3 Wood units, if precapillary pulmonary hypertension is not associated with lung disease, chronic thromboembolic pulmonary hypertension and other rare diseases had been excluded [1;2].

Thus, chronic thromboembolic pulmonary hypertension (CTEPH) is considered a unique and potentially curable form of pulmonary hypertension. CTEPH is characterized by mechanical obstruction of pulmonary elastic-type arteries due to organized blood clots. The pathophysiological basis is the formation of thrombotic masses not undergone lysis and then to fibrosis, which leads to mechanical obstruction of pulmonary arteries. The causes are alterations in coagulation cascade and clotting, including the dysfunction of endothelial cells and platelets [42]. Therefore, in contrast to PAH, patients with chronic thromboembolic pulmonary hypertension require life-long oral anticoagulants, including patients who previously underwent surgical treatment [43].

Four main pathogenetic mechanisms of PAH are known: vasoconstriction, reduction of the pulmonary vascular bed, decreased compliance of the pulmonary vessels, obliteration of pulmonary vessels (thrombosis in situ, proliferation of smooth muscle cells) (fig. 1). To date, processes that play a starting role in the development of pathological changes in the pulmonary vessels in pulmonary hypertension have not been determined. The modern theory of the pathogenesis of pulmonary hypertension focuses on the dysfunction of endothelium or its damage, leading to disruption of the balance between vasoconstriction and vasodilating substances and the development of vasoconstriction. The release of unidentified chemotactic agents from the damaged endothelial cells induces the migration of smooth muscle cells to the intima of pulmonary arterioles. Secretion of locally active mediators with a pronounced vasoconstrictor effect contributes to the development of thrombosis in situ, transforming the status of the pulmonary vascular bed from the normal anticoagulant state (due to the liberation of prostacyclin and inhibitor of tissue plasminogen activator) into the procoagulant. As a result, we see the formation of a vicious circle: damage of the endothelium steadily progresses and leads to remodeling of pulmonary vessels, increases vascular obstruction and obliteration. Thus, pathological processes involve all layers of the vascular wall and several cell types – endothelial, smooth muscle, and fibroblasts. There is an increased production of the extracellular matrix including collagen, elastin, fibronectin, and tenascin in the adventitia. Inflammatory cells and platelets also play a significant role in the development of pulmonary hypertension. In the blood plasma of patients with pulmonary hypertension levels of proinflammatory cytokines are increased, metabolism of serotonin is disturbed in platelets. Thus, the imbalance between thrombotic, mitogenic, proinflammatory, vasoconstrictive factors and reverse action mechanisms – anticoagulant, antimutagenic, vasodilating – promotes vasoconstriction and thrombosis, proliferative and inflammatory changes in the pulmonary microcirculatory bed [2].

The use of anticoagulants in patients with PAH has remained a contentious issue for decades.

Several clinical trials have shown a beneficial effect of anticoagulant therapy on the prognosis of patients with idiopathic pulmonary hypertension; however, most of these studies were

Pulmonary Arterial Hypertension: histopathological features

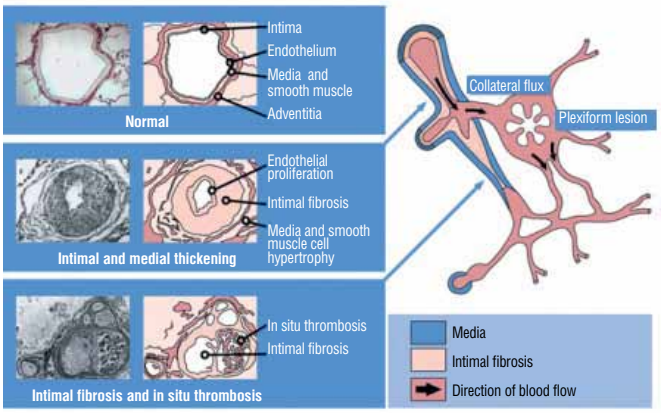

Figure 1. Pathogenetic aspects of pulmonary arterial hypertension

retrospective and had a small sample. Despite the lack of conclusive evidence, current recommendations suggest the use of anticoagulants in patients with idiopathic pulmonary hypertension, but at the same time, are vague on its use in other forms of PAH [3]. So, the situation is even less clear for patients with other forms of PAH for which there is almost no published evidence for or against the use of anticoagulants. Some of these patients are at increased risk of bleeding, especially patients with connective tissue diseases, congenital heart defects and liver diseases [4; 5; 6].

ORAL ANTICOAGULANTS IN PULMONARY HYPERTENSION

For a long time, the main oral anticoagulant used for the treatment and prevention of thrombotic complications was a synthetic antagonist of vitamin K –warfarin. It should be noted that at present, it remains the most commonly prescribed drug in this group. However, the risk of side effects, such as bleeding, difficulty in use (a prolonged period of restoration of normal coagulation after discontinuation, dosing and regular monitoring of the INR) have led to the need for more safe and convenient new oral anticoagulants (NOACs). Currently, there are three NOACs, registered in Russia: dabigatran, rivaroxaban, apixaban (table 1), where in a reduced risk of hemorrhagic events and not requiring INR monitoring (table 2).

Table 1. The pharmacokinetic properties of the NOACs (TCmax –time to reach maximum concentration in plasma, T1/2 – half-time elimination)

Drug	TCmax, h	T1/2, h	Bioavailability	Association with blood plasma proteins
Rivaroxaban	2-4	5-9 ч**	80-100%	92-95%
Dabigatran	0,5-2	12-14	6,5%	34-35%
Apixaban	3-4	12	50%	87%

M. Delbeck et al., used animal models to compare the effects of a direct inhibitor of Xa factor, rivaroxaban, to warfarin and enoxaparin on the prevention of dysfunction and hypertrophy of the right ventricle in monocrotaline model of pulmonary hypertension. Thus, the Sprague-Dawley rats (n=10 in each group) were randomized to receive either rivaroxaban, or warfarin, or enoxaparin, or placebo before receiving a subcutaneous injection of 60 mg/kg monocrotaline or saline. Rivaroxaban and enoxaparin were given for 28 days starting 4 h before the injection of monocrotaline; therapy with warfarin was continued for 35 days starting 7 days before the injection of monocrotaline. Hemodynamic parameters and parameters of hypertrophy were evaluated 28 days after administration of monocrotaline. Rivaroxaban dose-dependently

decreased systolic and decreased elevated end-diastolic pressure in the right ventricle and reduced right ventricular hypertrophy. Warfarin only reduced elevated blood pressure in the right ventricle. Enoxaparin did not affect any parameter. Serious bleeding occurred in four and five rats in warfarin and enoxaparin groups, respectively, whereas no bleeding was observed in rivaroxaban group. Thus, the authors concluded that selective, direct inhibition of factor Xa by rivaroxaban effectively prevented dysfunction, and right ventricular hypertrophy in rats, that received an injection of monocrotaline. This indicates the role of clotting factors in experimental pulmonary hypertension. Therefore, a clinical study on effects of early and continuous therapy of inhibitor of factor Xa, such as rivaroxaban, for PAH is advocated [41].

ORAL ANTICOAGULANTS IN IDIOPATHIC PULMONARY HYPERTENSION

In a number of studies, published mainly in the 1970s, C. A. Wagenvoort et al. described the thrombosis of small branches of pulmonary arteries as one of the typical histopathological features of idiopathic pulmonary hypertension at that time referred to as primary pulmonary hypertension [7; 8; 9]. This observation, along with studies, showing an increased blood clotting in patients with severe pulmonary hypertension, led to the hypothesis that thrombosis in situ in altered pulmonary vessels may contribute to the progression of the disease, and anticoagulant therapy might have had a positive effect [10; 11; 12]. Supporting this hypothesis, in 1984 V. Fuster et al., published the results of the observational study, which confirmed the presence of thrombotic pulmonary vascular lesions in patients with idiopathic pulmonary hypertension and showed, based on retrospective analysis of 120 patients, that the use of anticoagulants was associated with better survival [13]. Later S. Rich et al. also found survival rates to be higher among patients receiving anticoagulants. In this study, the indication for oral anticoagulants were abnormalities in lung perfusion on scintigraphy [14]. A systematic review of the literature found 7 studies, 5 of which showed that anticoagulant therapy had a positive effect and 2 – that effect was negative [15]. So far, there has been no prospective randomized clinical studies, evaluating the use of anticoagulants in patients with idiopathic pulmonary hypertension. There is a clear pathophysiological rationale for the use of anticoagulants in patients with idiopathic pulmonary hypertension, which is supported by preliminary clinical data, but the scientific evidence remains limited [3].

Given the scarcity of data supporting the use of anticoagulants in patients with PAH, an opposite opinion exists. The above mentioned evidence were obtained at the time when almost no pathogenetic methods of treatment of PAH were available. Wider use of effective specific therapy has led to improved hemodynamics, physical activity and survival in patients with PAH [16; 17]. At the same time, at least in Europe, the demographics of these patients has changed, and now PAH is often diagnosed in elderly patients with multiple comorbidities [18; 19; 20; 21]. Therefore, it is unclear how necessary is anticoagulant therapy is to these patients, especially when the incidence of bleeding in patients with idiopathic pulmonary hypertension is 5.4 in 100 years and 19 in 100 years in case of PAH, associated with connective tissue diseases [22].

K.M. Olsson et al. described the European COMPERA registry, which prospectively records patients with pulmonary hypertension. The sample included 1283 patients with newly diagnosed PAH. Anticoagulant therapy was used in 66% of 800 patients with idiopathic pulmonary hypertension, and 43% of 483 patients with other forms of PAH. Patients with idiopathic pulmonary hypertension had athree-year survival rate of anticoagulant therapy significantly higher compared with those who had never taken anticoagulants (P=0,006). Multivariate regression analysis confirmed the beneficial effect of anticoagulation on the survival in patients with idiopathic PAH (risk ratio, 0,79; 95% CI, 0,66–0,94). On the contrary, the use of anticoagulants in patients with other forms of PAH was not associated with increased survival, in fact, there was a trend towards worse outcomes in patients with PAH associated with scleroderma (P=0,08). Thus, these data favor the use of anticoagulants in patients with idiopathic PAH but not with other forms of PAH [3].

D. Caldeira et al. in a systematic review and meta-analysis sought to determine the effects of oral anticoagulants on survival in patients with PAH. However, no randomized controlled studies were found. So, in the meta-analysis were included 9 cohort studies: 2 prospective [14; 23] and 7 retrospective [3; 24; 13; 25; 26; 27; 28], including 1730 patients with PAH. Oral anticoagulation (warfarin) was associated with 31% mortality risk reduction (HR 0,69; 95% CI: 0,57-0,82; I2=28%). The sensitivity analysis showed similar results and no significant heterogeneity. Thus, the authors concluded that there is no randomized evidence to support the use of oral anticoagulants in patients with idiopathic PAH. The pooled results of cohort studies favor oral anticoagulants for improved survival. However, there is still a need for a pragmatic randomized evidence with a clear answer to this important clinical question [29].

ORAL ANTICOAGULANTS IN PAH ASSOCIATED WITH CONNECTIVE TISSUE DISEASES

It is known that systemic scleroderma is an autoimmune collagenosis, characterized by vasculopathy and fibrosis and occurring in more than 2 million people worldwide [30]. It is well established that PAH is one of the main causes of death in systemic scleroderma, which is 30-40% of all deaths from this disease [31; 32; 33]. Untreated PAH in systemic scleroderma quickly leads to fatality from right heart failure and arrhythmias [34].

Thrombosis in situ is a part of PAH, associated with systemic scleroderma. It manifests with venous and arterial thromboses of the peripheral pulmonary vessels of small caliber and shares common histological features with idiopathic pulmonary hypertension [35]. While several observational studies, including

Table 2. The NOACs compared with warfarin [45]

	stroke/ thromboembolism	ischemic stroke /not specified	Hemorrhagic stroke	Large bleeding	Bleeding of the gastrointestinal tract	Cardiovascular disease	Death from all causes
Dabigatran 150	↓ on 34%	↓ on 24%	↓ on 74%	equally	↑ relative risk on 50%	↓ relative risk on 15%	↓ on 12% p=0,051
Dabigatran 110	equally	equally	↓ on 69%	↓ on 20%	equally	equally	equally
Rivaroxaban	equally	equally	↓ on 40%	equally	↑ relative risk of 3 times	equally	equally, p=0,09
Apixaban	↓ on 21%	equally	↓ on 49%	↓ on 31%	equally	equally	↓ on 11%

the Australian cohort study of scleroderma, demonstrated a positive effect of anticoagulant therapy on survival of patients with PAH, other observational studies did not support this view [36; 37; 38; 3; 29]. Of note is that many patients included in these studies were not administered with adequate specific therapy for PAH, and most of them suffered from idiopathic PAH [29; 36]. In contrast, data from the Australian cohort study in scleroderma demonstrated positive impact on survival in patients receiving anticoagulants and adequate specific therapy for PAH. In the group of PAH associated with connective tissue disorders (95% of which were patients with PAH associated with systemic scleroderma), median survival was only 5 years, and there was an estimated five-fold reduction in mortality if warfarin was used, prescribedat the doctor's discretion for an average of 2,6±1,8 years [23].

A. Calderone et al. have presented an explanation and methodology of a phase III, randomized controlled trial that helps to assess the efficiency, safety and cost-effectiveness of anticoagulants in PAH, associated with systemic scleroderma.This study compares therapy with 2,5 mg of apixaban to placebo in parallel groups, randomized at a 1:1 ratio, in both groups the drug will be taken twice a day for 3 years as a supplement to ongoing oral specific therapy for PAH. The primary endpoint will be time to death or clinical deterioration of PAH. Secondary endpoints will include functional capacity associated with quality of life and occurrence of adverse events. Cost-effectiveness of anticoagulant therapy versus placebo will also be assessed. It should be noted, that this is the first clinical study, aimed at the evaluation of efficiency, safety, and cost-effectiveness of anticoagulant therapy, as a component of the treatment of the PAH, associated with systemic scleroderma. To minimize bios, the trial will be blind, randomized and placebo-controlled. The choice of apixaban at a dose of 2,5 mg twice a day as anticoagulant therapy is based on consideration of risk-benefit for PAH, associated with systemic scleroderma [39].

ORAL ANTICOAGULANTS IN PAH ASSOCIATED WITH CONGENITAL HEART DESEASE

Congenital malformations of the heart and its major blood vessels are the most frequentcongenital abnormalities. As a result of improved detection, approximately 90% of patients with congenital heart disease (CHD) reach adulthood. PAH develops in 10% of cases either rapidly or over time, this reduces the exercise tolerance and worsens the prognosis. Data on these patients is limited. An ongoing prospective registry of newly initiated therapeutic methods for pulmonary hypertension COMPERA includes adult patients with all forms of PAH, who receive PAH-specific therapy. Since the November 16th, 2012, in the database has beengathered data on 3642 patients with PAH and congenial heart disease making up 8% of all. The average age of these patients was 39 years, males of 39%, the average distance of test 6-minute walk was 370±102 meters, functional class NYHA I/II – in 39%, III in 59% and IV in 3% of cases. The average quality of life in visual analog scale of 100 points (EQ-5 D) was equal to 51. Patients with PAH and CHD in 80% of cases received monotherapy and 9% – a combined PAH specific therapy and in 11% – patients got drugs that are not related to the treatment of PAH. Only in 20% of cases, the patients received oral anticoagulants. It is assumed that the 4-year survival of patients with PAH-CHD was 79%, compared with 72% in patients with idiopathic PAH. According to the register, patients with PAH-CHD have reduced exercise tolerance and significantly reduced quality of life. They receive the combination therapy and oral anticoagulants less frequently than patients with idiopathic PAH, however, their survival rate is higher [40].

CONCLUSIONS

Thus, the problem of anticoagulant therapy in PAH patients remains relevant and has not resolved to the present time. Given the availability of proven pathogenic mechanisms of increased thrombosis in these patients, the majority of researchers tend to favor anticoagulant therapy. Taking into account the results obtained in animal models, and preliminary results of a randomized, placebo-controlled studies ofapixaban, a positive role for the prognosis and decrease of the risk of thrombotic events in patients receiving new oral anticoagulants can't be excluded, but this requires further clinical trials.

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