MONITORING THE EFFECTIVENESS OF ANTITHROMBOLYTIC PREPARATIONS IN THE TREATMENT OF CORONARY HEART DISEASE

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Abstract: The criteria for an "ideal" anticoagulant are formulated and the compliance of currently known direct anticoagulants with these criteria is shown. Current recommendations for laboratory monitoring of the effects of "old" direct anticoagulants (unfractionated and low-molecular-weight heparins) and new-generation direct anticoagulants (thrombin and factor Xa inhibitors)are presented in patients of different risk groups.

Keywords: unfractionated heparin, low molecular weight heparins, direct anticoagulants, laboratory monitoring, thrombin inhibitors, factor Xa inhibitors

INTRODUCTION

In recent decades, coronary heart disease has consistently occupied one of the leading places in the structure of referrals. Disability and mortality due to cardiovascular diseases (CVD) among a socially significant group of the population in economically developed countries of the world. According to WHO estimates, more than 17 million people die from cardiovascular diseases worldwide every year, including more than 7 million from CHD. Mortality from CHD in people under 65 years of age has decreased by 50% over the past 20 years, which should be associated with more active treatment of acute myocardial infarction (use of thrombolysis, early revascularization), but overall mortality from CHD remained unchanged. This is due to an increase in the group of older people, where mortality naturally increases, despite the use of modern medicines. Mortality from CHD in men under the age of 65 is 3 times higher than in women, after 65 years of age the mortality rate in both sexes is equalized, and after 80 years of age it becomes 2 times higher in women than in men. It is significant that in the population only 40-50% of patients with angina are aware of their disease. The pathogenesis of most CVD is based on acute or chronic myocardial ischemia, which leads to deterioration of the pumping function of the heart muscle, fatal rhythm disturbances, severe hypoxia, and severe metabolic disorders in the body. The search for new forms and methods of treatment and prevention of CVD of ischemic origin is a priority area in cardiology worldwide, but the mortality rate in this pathology remains at a high level. The main nosological unit of CVD of ischemic origin is ischemic heart disease (CHD) and, in particular, myocardial infarction (MI), rhythm and conduction disorders, and heart failure. Despite the possibility of early diagnosis of ischemic heart disease (angiocardiografia, helical computer tomography, scintigraphy of the myocardium with the use of contrast agents), and the use of modern medical technologies (balloon

angioplasty, stenting of the coronary arteries, aorta and mammarocoronary bypass grafting (CABG, SS), the availability of modern "line" drugs) due to various reasons it is quite difficult to reduce mortality and the incidence of complications from cardiovascular disease, especially in the early hours of the onset of the disease.Based on due to the multifactorial nature of the occurrence and development of CVD of ischemic origin, there has been an interest in solving this problem through the treatment and prevention of antithrombotic therapy.

Direct anticoagulant drugs are widely used for the prevention and treatment of thrombosis and thromboembolic. All of them have advantages and disadvantages when used in a particular group of patients. Numerous difficulties observed with the use of unfractionated heparin stimulated the search for new anticoagulants that would not lead to a high frequency of hemorrhagic complications, would not cause platelet activation, the development of thrombocytopenia, and would be convenient to use. Recently, a new generation of direct anticoagulant drugs has been synthesized — factor (P) Xa and thrombin inhibitors, which give hope that the development and introduction into clinical practice of a perfect (effective, safe and convenient to use) anticoagulant drug is possible. The review examines the main qualities of direct anticoagulants, advantages and disadvantages in clinical use, and methods for monitoring safety and efficacy. J. Hirsh etal. [7], S. Haas [8], and A. Turpie [9, 10] formulated criteria for an ideal anticoagulant:

- a single daily dose of the tablet form of the drug;
- high efficacy against thromboembolic diseases
- predictable response;
- minimal possibility of hemorrhagic complications;
- no need for routine laboratory monitoring
- wide therapeutic range;
- simple, uncomplicated dose selection;
- minimal interaction with the food or other medications taken;
- low level of binding to plasma proteins;
- effective inhibition of clotting factors.

In our opinion, the presence of an antagonist to the anticoagulant used should be added to this list. A new generation of direct anticoagulants is approaching these criteria. According to the mechanism of action, anticoagulant drugs are divided into direct and indirect anticoagulants. Direct anticoagulants include unfractionated heparin (UFH), low — molecular-weight heparins (NMH) (nadroparin, enoxaparin, dalteparin, etc.), and selective drugs that block thrombin or PCa. The latter

group of drugs includes specific thrombin antagonists-hirudin, bivalirudin (hirulog), argatroban, etc., direct thrombin inhibitors-dabigatran, etc., indirect or selective PCa inhibitorsΦXa-fondaparinux, indraparinux, idrabiotaparinux, etc., direct PCa inhibitorsΦXa-rivaroxaban, apixaban, edoxaban, etc. Direct thrombin and PCa inhibitors are prescribed per os. Other direct anticoagulants (heparins, specific thrombin antagonists, and indirect PCa inhibitorsΦXa) are administeredparenterally [11]. Heparins. The anticoagulant effect of heparin, both UFH and LMWH, is to reduce fibrin formation by inhibiting the function of thrombin (FIIa) and activated PCa. The anticoagulant effect of heparin occurs only if there is a sufficient amount of antithrombin (AT) in the blood. [12]. Heparin in combination with AT also inhibits other procoagulants— , such as FIXa, PXI, and PXIIa. In addition, the heparin—antithrombin compound can reduce platelet activity [13]. The molecular weight of heparins ranges from 2,000 to 30,000 Da, which is determined by the length of the mucopolysaccharide chain.Heparins have a relatively rapid onset of action and are often the first drugs to be used in acute thrombotic conditions. With subcutaneous administration of UFH (sodium heparin), the effect of the drug occurs in 40-60 minutes, the maximum concentration is observed in 3-4 hours, the total effect lasts 8-12 hours. The peak effect of heparin sodium after subcutaneous administration occurs in 2-4 hours, the duration of action is 4-6 hours [11].One of the undesirable effects of UFH with prolonged use in large doses is the depletion of AT, which can also cause a state of hypercoagulation and cause thrombosis. Patients receiving high doses of UFH (more than 35,000 units daily) are at high risk of developingя heparin resistance [15]. Potential causes of heparinizationdeficit at, due to hereditary or acquired deficiency (DIC-syndrome, nephrotic syndrome, enteropathy, reducing ATM on the background of long-term therapy with heparin consumption at), liver disease with impaired synthesis of at, increasing the rate of excretion of heparin; increases binding of heparin to plasma proteins (NFG binding of PF4 from platelets); high content ΦVIII; increased concentration of fibrinogen; resistance to heparin induced by drugs [15].

General characteristics of new direct anticoagulant drugs Direct thrombin inhibitors Specific thrombin antagonists, such as hirudin and bivalirudin (hirulog), lepirudin, etc., directly inhibit dissolved and bound thrombin in the clot. Their anticoagulant effect does not depend on AT. These drugs do not bind to plasma proteins, do not affect platelet aggregation, and do not cause гепарининдуheparin-induced thrombocytopenia [7]. While the therapeutic concentration of heparin suppresses only 20-40% of clot-bound thrombin, the therapeutic concentration of direct trombine inhibitors suppresses 70% of thrombin [4]. Dabigatran is an oral thrombin inhibitor, characterized by rapid absorption, lack of food and drug interaction. The anticoagulant effect begins as early as 0.5-2 hours after administration [12]. In addition, dabigatran has a low bioavailability (6.5%), low (34-35%) ability to bind to plasma proteins. Elimination of the drug occurs mainly throughici (85%) in

unchanged form [8]. PCa inhibitors. Indirect or selective PCa inhibitors ΦXainclude fondaparinux, indraparinux, идрабиотапаринуксand idrabiotaparinux. A randomized trial of its effectiveness in preventing thromboembolic complications in patients with atrial fibrillation compared to vitamin K antagonists (AMADEUS), however, was discontinued due to a significant predominance of bleeding when using the new drug, although it was no less effective. Clinical trials of this drug in another categoryof patients are ongoing [2]. DirectoralPCainhibitorsincluderivaroxaban, apixaban, edoxaban, and others. A large program of clinical experimental studies has shown that rivaroxaban is currently the optimal direct PCa inhibitor ΦXa. Take the drug once a day. Its anticoagulant effect does not depend on the level of AT. It is characterized by high (80-100%) bioavailability, rapid onset of action — after 2-4 hours, 92-95% of rivaroxaban binds to plasma proteins (albumin). Rivaroxaban has a dual path of excretion: urine (50%) and feces/bile (50%), period floors of vyvedeniya is 7-11 h [10]. Discussion on the issue of laboratory monitoring of new anticoagulants have resulted in the following consensus: in non-selective groups of patients, determination of the anticoagulant effect of the drug after the appointment of a therapeutic dose may be needed in special circumstances such as:

•ischemic cerebral vascular thrombosis (stroke)
• bleeding (as a complication of therapy);
• severe injury;
• elderly patient;
•progressive renal failure;
•progressive liver failure;
•significant drug interaction [7, 8].

CONCLUSION

Thus, in recent years, a number of new direct oral anticoagulants — thrombin and PCa inhibitors-have appeared and shown their effectiveness. Hundreds of studies have been conducted, many patients in different countries have already been treated, but there are a number of serious issues that need to be clarified, first of all, it is safety and effectiveness in patients of various risk groups. The researchers are faced with a difficult task, but there is hope that the search for the ideal anticoagulant will be crowned with success.

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