Aspirin Resistance in Patients with Chronic Coronary Syndrome

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Abstract

This review summarizes aspirin features, actions and resistance in patients with chronic coronary syndrome. As well, it describes mechanism of the aspirin action and possible ways and causality of the aspirin resistance. In addition, it shows how to assess the efficacy of the aspirin therapy in patients with chronic coronary syndrome.

Key words: *aspirin resistance; chronic coronary syndrome; platelet reactivity;*

Introduction

Heart disease is the main cause of mortality and morbidity worldwide[1]. Platelets play a central role in the pathophysiology of chronic coronary syndrome (CCS): platelet activation and aggregation is one of the key mechanisms of thrombus formation. In turn, thrombosis is the direct cause of virtually all occlusive vascular events[2]. Therefore, antiplatelet drugs play a significant role in the treatment of these diseases. For more than 50 years, aspirin has been known as a drug with antiplatelet properties, and is the most widely used antiplatelet agent in patients with CCS for the prevention of various thrombotic and vascular disorders. Until recently, it remained practically the only clinically effective antiplatelet drug. Currently, daily intake of aspirin is indicated for all patients with CCS[3]. In the following decades, a large number of laboratory and clinical studies were carried out, as a result of which not only the mechanisms of action of acetylsalicylic acid were elucidated, but also its side and dose-dependent effects and influence on the course and prevention of CCS[4].

Aspirin is one of the most widely used antiplatelet drugs, prevents the development of repeated myocardial infarction, stroke, sudden coronary death. However, in some patients, aspirin is ineffective. The development of recurrent thrombotic complications with aspirin therapy or aspirin resistance is an independent predictor of high coronary risk[5]. In recent years, it has been noted that in a number of patients, aspirin has a less pronounced antiplatelet activity. This phenomenon is known as aspirin resistance[6]. Some researchers consider the term "ineffectiveness of aspirin therapy" more accurate. Aspirin resistance is defined as: the inability of aspirin to protect the patient from thrombotic complications; lengthen bleeding time; suppress the biosynthesis of TXA2; suppress platelet function in one or more in vitro tests.

Aspirin resistance is classified as clinical or laboratory. The clinical type of resistance is said when, despite taking aspirin, thrombotic complications occur. Laboratory type of aspirin resistance is diagnosed based on the determination of platelet function in vitro while taking aspirin. At the same time, aspirin does not effectively suppress platelet function in all patients. There is evidence that aspirin does not work in a third of patients. There was a correlation between laboratory signs of aspirin resistance and the clinical course of ischemic heart disease.

The history of the development of the concept of "aspirin resistance" Prescribing aspirin, one should

expect lower (in relation to the initial) indicators of platelet aggregation. However, a number of studies have shown that the immediate "biological" effect of aspirin is not the same in different patients, which has led to the assumption of the existence of "therapeutic" resistance. Studies carried out by other authors have also suggested that the antiplatelet effect of aspirin may be heterogeneous in patients, and that a certain proportion of patients are "resistant" to aspirin. The first data showing a decrease in the effectiveness of aspirin in some patients was obtained among patients with cerebrovascular disease: in about a quarter, partial suppression of platelet aggregation was achieved, in a third of patients resistance to aspirin develops after a long time, even despite an increase in the dose of aspirin.

The use of various methods for assessing platelet function: bleeding time, flow cytometry, platelet aggregation confirms the variability of the antithrombotic response among patients to aspirin therapy. However, the lack of standardized diagnostic criteria or one validated method for identifying affected patients leads to a wide range of population estimates. Thus, it has been proved that there is a large category of patients with clinical manifestations of resistance to aspirin, who, despite taking this drug, develop ischemic complications.

Aggregation of platelets - the formation of platelet conglomerates in the blood plasma, occurs upon activation and interaction of GP-receptors IIIa / IIb through the formation of fibrin "bridges" between platelets. Adhesion - adhesion of platelet conglomerates to the damaged intima of the vessel, is controlled by von Willebrand factor (fWb). Thus, platelet activation is a key moment in the pathogenesis of CVC, which largely determines the severity of blood supply disorders to organs and tissues (heart, brain, peripheral vessels), therefore antiaggregatory therapy is pathogenetically justified. Currently, there are four groups of antiplatelet drugs, the division into which is based on the principles of evidence-based medicine, using the concepts of "effectiveness" and "safety". The first group of antiplatelet drugs, the use of which is not recommended for cardiology due to lack of advantages over acetylsalicylic acid (aspirin), ineffectiveness in cardiac situations and potential danger: dipyridamole, prostacyclin, thromboxane A2 synthetase blockers, thromboxane A2 receptor antagonists, platelet IIIa / IIb receptor inhibitors for oral administration. The second group, which forms the basis of modern antiplatelet therapy, are reversible and irreversible cyclooxygenase inhibitors, the latter being ASA (Aspirin). The third group - thienopyridines (clopidogrel) and the fourth group - blockers of HP-receptors IIIa / IIb for intravenous use in ACS (abciximab).

Several mechanisms have been described as potential causes of the laboratory phenomenon of aspirin resistance. A number of studies have demonstrated partial inhibition of thromboxane A2 synthesis in patients on aspirin with a high RPR, which corresponds to the term "aspirin resistance"[7,8,9]. The clinical significance of this phenomenon has been demonstrated in a number of studies[10]. However, current guidelines for the management of patients receiving aspirin do not recommend routine testing to determine platelet function[11]. Currently, other antiplatelet agents are available in clinical practice for long-term treatment of a patient with coronary artery disease. In the past decade, clopidogrel has been widely used in combination with aspirin in high-risk patients, often for a limited period of time[12]. Also, clopidogrel is used as monotherapy for contraindications to taking aspirin. For both drugs, high variability in RPR detection rates was demonstrated with these drugs. It has not yet been studied whether the optimal tactics of replacing aspirin with clopidogrel in patients with high RPR during treatment with aspirin[13].

The prevalence of resistance to aspirin therapy, according to various studies, ranges from 10 to 40%[14]. Possible reasons for this phenomenon include the following:

1. Pharmacodynamic interactions of ASA with NSAIDs.

2. The presence of non-platelet sources of thromboxane A2 synthesis (endothelium, monocytic / macrophage cyclooxygenase-2 - COX-2).

3. Expression of COX-2 in newly formed platelets.

4. Hydrolysis of ASA by esterases of the gastrointestinal mucosa.

5. Increased synthesis of thromboxane A2.

6. Hyperlipidemia.

7. Genetic features.

There is reason to believe that resistance to aspirin therapy may be associated with a polymorphism of the cyclooxygenase gene affecting the active site of the enzyme (Ser529), a polymorphism of genes encoding other enzymes involved in the mobilization and metabolism of arachidonic acid (phospholipase, thromboxane synthetase) and polymorphism of genes encoding others GP – platelet receptors[15]. However, true resistance is rare and, as a rule, the failure of ASA treatment is associated with low compliance.

Thus, it can be argued that the presence of resistance to aspirin significantly increases the risk of cardiovascular events and the prevention of thrombosis, which is a key moment in the development of CCS, with the help of antiplatelet drugs, is the defining direction in the treatment of patients in therapeutic and surgical practice. Aspirin contribute to the active prevention of thromboembolism, and their combination can reduce the amount of drug taken with an increase in therapeutic activity and a decrease in side effects.

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