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Role of the acetylsalicylic acid in the treatment of coronary artery disease.

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Abstract

Coronary artery disease (CAD) is leading due to disability and death of the working population, and successful its treatment is largely determined by maintaining adequate coronary blood flow, including through interventions, percutaneous interventions. Acetylsalicylic acid is widely used in patients with coronary artery disease (CAD) to prevent major adverse cardiac events (MACE). Lately, attention is increasingly being paid to the variability of the response to antiplatelet therapy. High platelet reactivity increases the risk of ischemic events. The causes of resistance to antiplatelet agents are heterogeneous and multicomponent: clinical, cellular and genetic. This review article describes features and characteristics of the using acetylsalicylic acid- aspirin in CAD, as well as current problems in the antiplatelet therapy.

Keywords: Aspirin, Coronary artery disease, Antiplatelets.

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Introduction

Coronary artery disease (CAD) is leading due to disability and death of the working population, and successful its treatment is largely determined by maintaining adequate coronary blood flow, including through interventions, stenting of coronary arteries (CA) [1]. An increased risk of developing coronary artery disease and other manifestations of atherosclerotic vascular lesions is associated with a resistance to the antiplatelet therapy particularly in aspirin, as well as abnormal blood lipid components [2]. A serious problem for patients with CAD after endovascular intervention is the prevention of thrombosis of stented coronary arteries. For this purpose, patients are prescribed two-component antiplatelet therapy (DAT), including clopidogrel and acetylsalicylic acid (ASA) preparations [3].

Review

Treatment strategy in patients with CAD includes the use of optimal drug therapy (OMT) and the use of invasive treatment methods. Moreover, in the case of acute forms of coronary heart disease, such as myocardial infarction (MI), invasive treatment tactics are preferable to the use of OMT, and in chronic cases of coronary heart disease, the use of OMT is advisable. Modern OMT IHD includes the use of the following classes of drugs: antiplatelet drugs, Lipid-lowering agents (statins, etc.), Angiotensin converting enzyme inhibitors (ACE inhibitors) Antianginal drugs (such as, β-blockers, calcium antagonists, nitrates, ivabradine - an inhibitor of If-current of the sinus node cells, potassium channel activator - the drug nicorandil and myocardial cytoprotect ortrimetazidine).

The use of aspirin is aimed at one of the most important pathogenetic links of CAD - treatment and prevention of atherothrombosis. Aterothrombosis develops as a result of damage to the surface of the atherosclerotic plaque, which leads to the development of thrombosis on its surface, which completely or partially narrows the lumen of the artery [4]. Platelets that come into contact with the subendothelial layer play a key role in this process. The interaction of platelets with collagen and the von Willebrand subendothelial factor causes their adhesion to the vascular wall at the site of damage to the endothelium. The binding of von Willebrand factor to the glycoprotein receptors of the platelet Ib membrane is accompanied by the formation of a signal that is transmitted into the cell and causes expression of the IIb/IIIa glycoprotein receptors on the platelet membrane. Platelet activation agonists are collagen of the subendothelial matrix, thrombin, thromboxane A2, adenosine diphosphate, serotonin, and norepinephrine. Activated glycoprotein receptors IIb/IIIa have an increased affinity for the molecules of adhesive proteins (fibrinogen, fibronectin, von Willebrand factor), which form protein bridges between cells, resulting in the formation of a platelet aggregate. The content of calcium ions increases in the activated platelet, which potentiates the secretion of ADP, serotonin and the formation of thromboxane A2. The release of these compounds from granules of activated platelets leads to the activation of other cells and their involvement in the formation of the primary platelet, or “white”, thrombus. Aspirin blocks platelet activation by inhibiting cyclooxygenase-1 (COX-1), as a result of which the transformation of arachidonic acid into prostaglandin H2 is disrupted, from which thromboxane A2, in turn, is not formed. Platelet function is currently being evaluated in clinical trials, but not in routine clinical practice. Several studies are needed

to address the routine assessment of platelet function and the individual selection of antiplatelet therapy based on these tests. The search for various combinations of drugs aimed at suppressing this activation has led to the fact that for more than 15 years, double antiplatelet therapy in the form of aspirin in combination with clopidogrel has been the "gold standard" in coronary angioplasty. Nevertheless, in recent years, more and more attention has been paid to the question of the variability of the response to antiplatelet therapy [5]. High platelet reactivity increases the risk of ischemic events.

There are other mechanisms of action of aspirin, in which it differs from other antiplatelet drugs. Aspirin has an inhibitory effect on the formation of fibrin by suppressing the formation of thrombin (FII>FIIa) and the functional state of fibrinogen - FI (blocks lysine in fibrinogen molecules). At the same time, aspirin is able to activate fibrinolysis through the release of plasminogen activators with the "loosening" of fibrin fibers. Complete suppression of thromboxane production is achieved with continuous long-term administration of aspirin in doses of ≥ 75 mg/day. Thus, in most patients with stable coronary artery disease, it is preferable to prescribe low doses of aspirin, which reduce the risks of haemorrhagic complications. It is important to remember that the damaging effect of aspirin on the digestive tract increases with increasing dose.

However, blocking only one platelet activation pathway associated with inhibition of COX and the formation of thromboxane A2, aspirin certainly cannot solve all the problems of antithrombotic therapy in patients with acute coronary syndrome.

In addition, in a number of independent studies of acute coronary syndrome without ST segment elevation on an electrocardiogram - ECG (ESSENCE, PISM PLUS), it was found that the immediate prognosis depends on the previous intake of ASA before the development of an exacerbation of CAD. So, in the PRISM PLUS study with ASA in acute coronary syndrome, the incidence of MI, refractory angina pectoris and sudden death by the 7th day of observation was 12.1% among patients who had not previously taken ASA, and 23.5% among people taking ASA before the development of exacerbation. This fact was called the “aspirin paradox”, which served as a reason for D. Bhatt and E. Topopol (2003) to classify ASA as “suboptimal antiplatelet agents” [6]. We must not forget the fact that, according to different authors, the number of ASK-resistant individuals ranges from 5% to 40%, while the number of ASK-resistant patients is the highest among patients with exacerbations of coronary heart disease, developed against the background of its constant use. There is reason to believe that the number of patients resistant to ASA increases with increasing duration of its use. Currently, the following main reasons for the development of clinical and laboratory resistance to ASA are distinguished [6]: decreased bioavailability of ASA (inadequate dose of the drug: decreased absorption or increased metabolism of the drug), impaired binding to COX-1 (concomitant use with other non-steroidal anti-inflammatory drugs, which hinder the access of ASA to COX-1 receptors), the presence of non-platelet sources of thromboxane A2 synthesis (vascular endothelium, monocytic/macrophage COX-2), alternative pathways of tro activation of bocytes (induced by red blood cells, stimulation of collagen, ADP, adrenaline, thrombin receptors on platelets), increased “circulation” of platelets (increased production and release of platelets by the bone marrow in response to stress, for example, after aortocoronary bypass surgery), genetic polymorphism (CO) COX-2, thromboxane A2 synthetase and other enzymes involved in the metabolism of arachidonic acid and hemostasis factors), loss of antiplatelet effect of ASA with prolonged use, hyperlipidemia, smoking. The problem of resistance to ASA is complicated by the fact that there are currently no reliable tests to confirm aspirin resistance.

In addition, one of the problems associated with prolonged use of ASA is damage to the gastrointestinal tract (GIT), especially the stomach. ASA inhibits the activity of the COX enzyme that protects the gastric mucosa by synthesizing prostaglandin PgE2, which leads to side effects such as the formation of gastric mucosa ulcers and bleeding. For quite a long time, many clinicians considered the use of enteric-soluble forms of ASA to be the only and almost 100% solution to this problem [7]. However, according to the results of recent studies, the formation of erosion and gastric ulcers is noted even with aspirin coated with an enteric coating, which scarred in 90% of cases with cimetidine and antacids only after the cancellation of these forms of aspirin [8]. In addition, contraindications for taking ASA are expressed: severe allergy in the form of attacks of bronchospasm (including bronchial asthma, combined with polypus rhinosinusopathy and intolerance to the drug, “aspirin asthma”); hemophilia and thrombocytopenia; active bleeding, including retinal hemorrhage; erosive and ulcerative processes in the digestive tract or other sources of bleeding from the digestive tract or urinary tract; severe uncontrolled arterial hypertension; severe renal and liver failure.

As for the use of ASA in patients with coronary heart disease who underwent percutaneous coronary intervention (PCI), the use of this drug is advisable in all cases [9]. Thus, according to the European recommendations for the treatment of patients with acute coronary syndrome without ST segment elevation, ASA at a loading dose of 150-300 mg is recommended for all patients who have no contraindications, then it is necessary to continue taking ASA at a dose of 75 – 100 mg/day, regardless from the chosen treatment strategy (evidence class IA). In the American guidelines for the treatment of patients with myocardial infarction with ST elevation [10], prolonged, for 12 months, combination therapy with ASA and a P2Y12 receptor inhibitor is recommended for all patients who underwent primary PCI (IB). In the American Recommendations on PCI (18), after planned PCI with a stent implantation, all patients are recommended to take ASA in a maintenance dose for an indefinitely long time (IA) and clopidogrel in a maintenance dose for up to 12 months, in the absence of a high risk of bleeding (IB). It is important to remember that before implanting coronary stents, especially drug-coated stents, patients should be examined for the need for a long time of double antiplatelet therapy and to assess the risk of bleeding. The dose and duration of ASA intake depend both on the type

of stent and on the risk of bleeding in this patient. In the early period after stenting, patients should take ASA in an increased dose of 162 – 325 mg/day - after implantation of a holometallic stent - 1 month, drug-coated stent 3-6 months (depending on the medicine). Subsequently, its intake should be continued on an on-going basis at a dose of 75 – 162 mg/day, regardless of the type of stent. In case of an increased risk of bleeding, it is allowed to use ASA at a dose of 75 – 162 mg/day and immediately after stenting.

The main limitation in the use of ASA, as well as any other non-steroidal anti-inflammatory drugs (NSAIDs), are gastrointestinal complications in the form of dyspeptic disorders, erosive and ulcerative gastritis and, accordingly, a high risk of bleeding. According to various authors, in patients with acute coronary syndrome, gastroduodenal "stress" injuries of the mucous membranes develop in 8% – 25% of cases. According to the results of one clinical and morphological studies, among patients who died from acute myocardial infarction, in 10% of cases, signs of damage to the mucous membrane of the upper gastrointestinal tract were detected [11]. It was also shown that of patients coming to the hospital with a diagnosis of acute gastrointestinal bleeding, more than half took NSAIDs. Lesions of the large and small intestines while taking NSAIDs are much less studied, but their frequency of occurrence is much lower. If an ASA-induced gastrointestinal lesion occurs, gastroprotective therapy is necessary with the decision on the possibility of canceling ASA. The decision to cancel the ASA should be made on the basis of an assessment of the risk and benefit for the patient in each case. The enteric forms of ASA currently used are significantly reduced the risk of damage to the gastric mucosa and the occurrence of gastrointestinal bleeding. According to domestic authors, in a study that included 80 patients with coronary artery disease, a history of myocardial infarction and a high risk of developing gastropathy, as a result of a 3-month therapy with an enteric-soluble form of ASA or a drug containing an non-absorbable antacid, not a single case of gastric or gastric ulcer was recorded intestinal bleeding [12]. The enteric coating makes ASA safer for the stomach, but delays the onset of the drug by an average of 2 hours. Thus, aspirin is a drug that minimizes the adverse effect on the gastric mucosa, whose effectiveness has been proven for primary and secondary prevention of cardiovascular diseases.

Conclusion

In conclusion, one of the leading areas in the pharmacotherapy of coronary artery disease and the prevention of the development of myocardial infarction is the rational administration of aspirin. Of great importance is the increase in the number of patients with atherothrombosis receiving prophylactic modern antiplatelet drugs, which will improve the prognosis for this pathology, which requires more information for doctors and patients about modern antiplatelet agents and their clinical and economic effectiveness from the standpoint of evidence-based medicine and pharmacoeconomic analysis.

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