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FACTORS INFLUENCING THE EFFECTIVENESS OF ANTIPLATELET THERAPY

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ABSTRACT — In recent years, significant advances in the diagnosis and treatment of cardiovascular diseases have been achieved in the healthcare of most countries. However, among the causes of mortality in patients with coronary heart disease, arterial thrombosis takes one of the leading positions. Antiplatelet drugs are prescribed to prevent thrombotic complications, which can be used as mono- or two-component therapy. In case of atherosclerosis in arteries, acetyl-salicylic acid (ASA) or clopidogrel can be used as monotherapy; treatment of acute coronary syndrome (ACS) and percutaneous coronary interventions (PCI) required using of double antiplatelet therapy (DAT), including acetylsalicylic acid drugs together with one antiplatelet agent from the group of thienopyridine derivatives — blockers of P2Y12 platelet receptors (clopidogrel, ticagrelor, prasugrel).
In patients with ACS who underwent primary PCI or thrombolysis followed by PCI, the duration of DAT is 12 months, and clopidogrel is the drug of choice [16, 30]. According to various literature sources about 20–40% of patients have low effectiveness of antiplatelet therapy, which can lead to thrombosis, stent thrombosis and thromboembolic complications. This review provides an analysis of modifiable and nonmodifiable factors contribution to the development of clinical and laboratory resistance of antiplatelet agents.

KEYWORDS — acute coronary syndrome, acetylsalicylic acid, clopidogrel, biotransformation genes, clinical and phenotypic features.

INTRODUCTION

All over the world, mortality from cardiovascular diseases remains extremely high, re-gardless of recent years achievements related to the development of new methods of diagno-sis, treatment, updating of clinical recommendations and treatment protocols.

In Russia, at least 49% of all patients die due to cardiovascular diseases, among which coronary heart disease is determined as the cause of death in 28.4%, and cerebrovascular diseases (including stroke) — 14.4% [50]. More than 54 thousand people died from a heart stroke in Russia in 2019 only according to Rosstat data.

For all patients with coronary heart disease: stable angina pectoris, ACS with and without ST segment elevation, antiplatelet agents are an essential part of treatment. It should be realized that long-term administration of antiplatelet agents is always a fine balance be-tween thrombosis and bleeding. On the one hand, it can be explained by the complexity of the thrombosis chain and the complexity of acting simultaneously on all components that trigger and support the process of blood clot formation. On the other hand, a variety of scientifically and clinically proven exogenous and endogenous factors can influence the individual respon-siveness of patients to antiplatelet therapy.

In patients resistant to antiplatelet therapy, there is an increase in the frequency (2.5–3.5 times) of myocardium infarction, ischemic strokes compared to patients susceptible to it, which makes extremely relevant the problem of antiplatelet agent's resistance develop-mentstudying [13, 15, 17].

The aim of this review was to summarize the available results of foreign and national studies devoted to the study of the antiplatelet drugs resistance development.

MATERIALS AND METHODS

For this review we used data of scientific publications from open and accessible sources in the period 2001–2021, published in electronic databases: pharmgkb.org, PubMed, Scopus, Web of Science Core Collection, Elibrary, Google Scholar. Search queries — "anti-aggregational therapy + therapy resistance", "COX polymorphism + aspirin resistance", "GPIa gene polymorphism, P2Y1 + aspirin resistance", "CYP2C19+clopidogrel+ antiplatelet therapy efficacy"; "clopidogrel resistance + CYP2C19 polymorphism" in both Russian and English.

RESULTS AND DISCUSSION

Antiplatelet therapy resistance

The efficacy of ASA low doses prescribing in patients with coronary heart disease has been confirmed

in more than 200 studies conducted over the past 30 years [26]. The role of ASA as a secondary prevention drug has been conclusively demonstrated, which reduces the chance of serious cardiovascular events over 25%.

The mechanism of ASA antiplatelet effect is the inhibition of COX-1 formation and the of thromboxane A2 (THA2)synthesis, which leads to a decrease in the residual platelet reactivity. Optical aggregometry, also called light transmission aggregometry, is the *gold standard* in evaluating the influence of aspirin on platelet reactivity.Such methodin the presence of unquestionable advantages, has a number of disadvantages, including related to the complexity of the process. Currently, portable devices such as optical detection of platelet agglutination (VerifyNow) have been introduced into practical healthcare to evaluate platelets reactivity directly at the patient's bedside.

Overall, ASA resistance is defined as *the inability of ASA to protect a patient from thrombotic complications; prolong bleeding time; inhibit THA2 biosynthesis; inhibit platelet function in one or more in vitro tests* [38].

However, there are differences between laboratory and clinical resistance. Laboratory resistance refers to the lack of residual platelet reactivity (RPR) blocking effect.Clinical resistance suggests the development of atherothrombotic events on the background of the ASA use [20, 21, 22].

Among the causes of clinical resistance to ASA, the following are identified: defects in the effect on a specific platelet receptor, ineffective acetylation of COX-1 and lack of thromboxane A2 (TXA2)inhibition[37].

There are studies confirming the involvement of the ASA taking duration factor in the development of resistance to aspirin. Thus, according to Pulcinelli F.M. et al., in 150 patients, despite an adequate decrease in aggregation 2 months after the start of ASA treatment, a permanent decrease in sensitivity to it was observed in the longer term [40].

The classification of resistance to ASA suggested by Weber AA in 2002 also makes it possible to identify the pharmacokinetic, pharmacodynamic type and *pseudo-resistance*.

The first type includes cases of ASA platelet aggregation activity (PA) suppressionand synthesis of TXA2 only in vitro. With the pharmacodynamic type, it is not possible to suppress PA in vitro or in vivo. All cases of "*thromboxane-independent platelet aggregation*" belong to the *pseudo-resistance* to ASC, when high residual platelet reactivity (HRPR) persists with adequate pressure of TXA2 biosynthesis [46].

It is explained by the fact that in addition to platelet activation by stimulation of thromboxane A2 receptors, there are alternative activation pathways, including stimulation of platelet membrane glycoproteins (platelet receptors) by collagen (GPIa/IIA), von Willebrand factor (GP Ib/V/IX), ADP, thrombin, epinephrine, serotonin [5, 11, 13].Moreover, it was found that in patients in the early post-infarction period there is a possibility of platelet activation through Toll-like receptors 2/1, which is not stopped by standard antiplatelet therapy [31].

Clopidogrel resistance

Large placebo-controlled trials of the last 15–20 years have proven the advantage of clopidogrel as a supplement to aspirin as part of dual antiplatelet therapy (DAT) in ACS, which was confirmed by improved treatment results after PCI in both the short and long term, which marked the beginning of DAT active clinical use [28, 36, 41, 44, 48].

Today, clopidogrel is the most frequently prescribed drug in the group. Regardless to the large number of studies confirming the individual variability of the response to clopidogrel and the presence of ethnic specificity in the distribution of polymorphic alleles frequencies of enzyme gene that metabolizes it into the active form, clopidogrel does not cause such a large number of bleeding compared to its analogues. Clopidogrel is a prodrug, which requires its transformation in the liver to an active metabolite. Absorption of the drug in the intestine takes place with the involvement of P-glycoprotein, the synthesis of which is regulated by the MDR1 (ABCB1) gene. In the case of ABCB1 (CC, CT, TT) gene polymorphic alleles carrying, the activity of clopidogrel during absorption can change.Approximately 85% of the absorbed drug is inactivated by liver enzymes, while 15% with the involvement of cytochrome P450 isoenzymes CYP1A2, CYP2B6 and CYP2C19, are converted into an intermediate metabolite of 2-oxo-clopidogrel (thiolactone). Further, an active compound R130964 is formed from an intermediate inactive metabolite, mainly with the involvement of CYP2C19, which inhibits platelet aggregation by irreversible blockade of ADP P2Y12 on the platelet surface [8, 18].

Clopidogrel resistance refers to the drug's inability to block the target P2U12 receptor and effectively suppress platelet aggregation. Currently, the factors affecting the metabolic processes of clopidogrel at all its stages and the reasons that reduce its effectiveness have been established. Hereditary factors of the defect in the clopidogrel active metabolite formation, clinically significant interactions with other drugs that are inhibitors of CYP2C19, ethnicity, smoking, hyperglycemia, hypercholesterolemia, obesity, age, etc. are intensively discussed [49].

According to various meta-analyses, the average rate of clopidogrel resistance is 21% [44]. The prevalence of resistance to ASA varies quite widely between 2 and 43% [38]. Up to 6% of patients may have an insufficient response to dual antiplatelet therapy (aspirin + clopidogrel) [27].

The presence of laboratory resistance to ASA and/or clopidogrel enhances the com-parative risk of repeated cardiovascular events up to 4 times [CI 2.9; 5.6] over 18 months of follow-up, compared with a group of individuals not showing signs of resistance to antiplate-let agents [10].

Genetic, unmodified factors affecting responsiveness to antiplatelet therapy

In order to assess the contribution of hereditary factors to the formation of ASA resistance, the polymorphisms of the COX-1 genes were most fully studied: C22T, C50T/A842G, G128A, C644A, C714A, C10427A, G1446A, G765C; GPIa gene — polymor-phism C807T; GPIba — C5T gene; GPIIIa — T196C GPVI — T13254C gene; P2Y1receptor gene — C893T; P2Y1 — A1622G; P2Y12 — H1/H2 [3, 4].

Thus, it was found that in the examination of two single-nucleotide polymorphisms A-842G and C50T COX-1 in heterozygotes according to the haplotype A-842G/C50T, significantly greater inhibition (p=0.01) of ASA formation of prostaglandin was observed compared with homozygotes according to the wild allele [34].

Yi.Xingyang et al. (2017) revealed that arachidonic acid and ADP induced significantly greater platelet aggregation in patients with point mutations (including rs20417, rs1371097, rs2317676) of the GPIIb/IIIa gene than in patients without these genotypes. It was suggested by the authors that the combination of rs20417, rs1371097 and rs2317676 may potentially lead to initially high platelet aggregation among these people, thereby increasing the risk of aspirin resistance and early cardiovascular complications [47]

In a study of T. Goodman et al. (2008) a particular association was found between the carrier of the PlA1/A2polymorphic variant and resistance to aspirin in healthy people, and the effect decreased in the presence of cardiovascular diseases [33].

According to Kapustin S.I. (2017), in patients with deep vein thrombosis (DVT) and pulmonary embolism (PE), a more than 10-fold rise in the proportion of P2Y12 H2 variant homozygous carriers of the platelet receptor ADP gene was found — 3.4% versus 0.3% in patients with isolated DVT, OR = 10.7, 95% CI: 1.2 — 97.0; p = 0.023) [7].

In developing personalized approaches to clopidogrel usage, a lot of attention is paid to the polymorphic carriage of the CYP2C19 gene [1, 6, 8, 18]. The results of fundamental studies devoted to the evaluation of individual responsiveness to antiplatelet agents under the guidance of Professor D.A. Sychev are widely presented in the publications [18, 19, 23].

According to the results of the multicenter GRAVITAS study (USA), which examined 1152 blood samples and 40 polymorphisms, including CYP2C19 *2, *3 *4, *5, *6, *7, *8, and *17; ABCB1 and PON1, it was found that patients with one or two polymorphic alleles of the CYP2C19 gene, at which its functional activity is lost, do not respond even to a double dose of clopidogrel. There was an 11-fold rise in the risk of a sustained increase in platelet reactivity for 30 days in patients with homozygous carriers of the CYP2C19*2 gene, compared with patients who had a functionally active wild type gene. Heterozygotes also retained HRPR — up to 62% compared to carriers of the wild, rapid allele [39].

A genome-wide association GWAS study carried out by the International Pharmaco-genetic Consortium (ICPC) has shown that the response to clopidogrel has significant variability. In this case, according to the authors, alleles of CYP2C19 function loss make up only a certain part in the structure of the low response causes to the drug. The study involved 2750 people of Europeans whose DNA was tested. The GWAS study did not reveal any other SNP, except for CYP2C19*2, which would have reached genome-wide relevancy [45].

An association was found between the CYP2C19 genotype and the fact of the *end-point* of cardiovascular death, non-fatal myocardial infarction in young patients who had suffered a myocardial infarction and received clopidogrel in a dose of 75 mg/day. It was found that in patients with CYP2C19*2 genotype (28%), the risk of recurrence acute coronary event during the first year was several times higher than in patients with wild genotype. Moreover, the authors have positioned the cyp2c19 genotype polymorphism as the only sig-nificant predictor of the primary outcome in this patient population [29]

A study was conducted in Europe in patients with myocardial infarction (MI) with ST segment elevation and without ST elevation (n=2208 people) treated with clopidogrel [42]. All patients were genotyped for the following genes: CYP2C19; CYP3A5; ABCB1; P2Y12, P2RY12; ITGB3 (IIB–IIIA receptor).The frequency of CYP2C19 alleles*2, *3, *4 and *5 occurrence was studied for CYP2C19. A criterion which was used in this study is the *end point* or the primary result, which included death from any causes (strokes, myocardial infarctions, stent thrombosis, etc.) during the first year after the MI. Among patients with

cardiovascular events and thrombotic complications, the frequency of single-nucleotide polymorphisms in the CYP3A5, P2RY12 and ITGB3 genes was significantly higher (in comparison with group without the *end point*). Patients with two alleles of the CYP2C19 gene were more at risk of *end point* developing than in the group of patients not carrying polymorphic alleles [42].

The influence of clinically significant alleles variants of the CES1, PON1, ABCG2, CYP4F2, CYP3A4, IGTB3, P2Y12, PEAR1, B4GALT2 genes carriage on the antiplatelet effect of clopidogrel and clinical outcomes of patients with ACS and atrial fibrillation was studied. It was found that CYP4F2 C(VAL433MET), PEAR1 rs41273215 C>T polymorphisms were statistically significantly associated with a higher frequency of significant bleeding on the background of antithrombotic therapy (p=0.008;p=0.035). The polymorphic variant CT+TT B4GALT2 rs1061781 was significantly associated with an increased frequency of strokes and TIA (p=0.041) [23]. The research for new predictors of the formation of the HRPR continues.

The modern direction of the HRPR genetic predictors research is the study of the plasma microRNAs expression levels. Thus, a correlation was established between the level of plasma microRNA expression and the indicators of residual platelet reactivity in patients taking P2Y12 receptor inhibitors [19].

Modifiable factors affecting antiplatelet therapy responsiveness

Possible causes of aspirin resistance associated with insufficient compliance to therapy, low bioavailability of drugs, inadequately prescribed dose, poor intestinal absorption, clinically significant interactions with other drugs, functional immaturity of platelets, smoking, hypercholesterolemia, hyperglycemia, obesity, stress, comorbid pathology, high levels of pro-inflammatory cytokines, which are an additional source of thromboxane TXA2 and other fac-tors have been widely discussed in the publications [14, 20, 21, 22, 24, 49].

The patient's compliance to therapy is of great importance in achieving an adequate antiplatelet effect. The credibility and professionalism of the doctor largely determines how much the patient will follow all the prescribed recommendations on the dosage of the drug, the intake regimen, interaction with food etc., which finally will certainly affect the effectiveness of the prescribed drugs. Some studies have shown how the regularity of admission is influenced not only by motivational factors, but also by the packaging features that provide simplicity and convenience of admission. Thus, with the use of a calendar blister in elderly and geriatric people, the level of compliance was higher than in receiving drugs in an ordinary bottle.

Co-administration of antiplatelet agents with calcium channel blockers, beta-blockers, statins, may lead to a change in the efficacy and safety profile of antiplatelet agents, due to the effect on the functional activity of P glycoprotein, which ensures the drug absorption. In proton pump inhibitor therapy, hydrochloric acid production decreases and the pH increases above the dissociation constant of acetylsalicylic acid (3,5), which converts aspirin into an ionized state, lowering its lipophilicity and absorption.

The dose of the prescribed drug also affects the bioavailability. In 2002, a meta-analysis of the Antithrombotic Trialists Collaboration was published, summarizing the results of 287 randomized trials involving 135 thousand patients who had suffered some kind of cardiovascular event. It has been shown the use of ASA in a dose of 75–150 mg leads to a signif-icant decrease in the risk of repeated cardiovascular events in general by 25%, nonfatal myocardial infarction — by 30%, nonfatal stroke — by 25%, cardiovascular mortality — by 17% [26]. There are references in the publications to the administration of higher doses of ASA, proba-bly to increase bioavailability and provide a better antiplatelet effect, but the inhibition of TXA2 is completely dose-dependent and is implemented in the range of minimum doses — 75–150 mg.

Hyperglycaemia and obesity contribute to a decrease in the platelet activation endothe-lial inhibitors levels and, as a result, increase the risk of thrombosis. Elevated levels of glucose and hyperinsulinemia in platelets lead to activation of protein kinase C, a decrease in NO synthesis and an increase in oxygen synthesis [2]. Platelet membrane contains glycoproteins (GP) — receptors of adhesive proteins. In patients with metabolic syndrome (MS), there is an increased expression of glycoprotein Ib (GPIb) on the platelet surface, which determines platelet binding to the Willebrand factor. The interaction of GPIb and Willebrand factor induces an intracellular signal that leads to the activation of the GP IIb/IIIa complex, which allows the binding of plasma fibrinogen and Willebrand factor. At the same time, there can be a decrease in endothelial antiplateletfactors — nitrogen oxide and prostacyclin, and an increase in the formation of platelet activators [2, 11, 13, 25.]

The results of clopidogrel's antiplatelet effect studied in patients with obesity are presented. It appeared that the frequency of clopidogrel resistance in patients with obesity was significantly higher (60.8%) than in non-obese patients (35%; p=0.014). Resist-

ance to clopidogrel in patients with diabetes mellitus was also significantly more frequently recorded: in 18 (66.7%) people compared to 29 (39.7%; p=0.017) [14, 15].

A rise in the level of inflammatory markers, which include C-reactive protein (CRP), interleukin 6 (IL-6), IL-10, CD40, tumor necrosis factor (TNF), fibrinogen, can also lead to HRPR. This is explained by the fact that inflammatory mediators are alternative non-platelet sources of TXA2 [14, 15].

Smoking is another factor affecting the effectiveness of antiplatelet therapy. The effect of nicotine increases cholesterol levels, promotes atherosclerosis, is a risk factor for the development of cardiovascular diseases and sudden cardiovascular events. In recent years, so-called *smoker's paradox* has been discussed in the publications [9].A number of studies, including a meta-analysis carried out by J. J. Gagne et al., showed how the use of clopidogrel was associated with a decrease in the frequency of the combined endpoint, including death from cardiovascular causes, myocardial infarction and stroke, by 25% in smokers and only 8% in non-smoking patients [32].Certainly, such observations set a certain dilemma for specialists and require more in-depth research into this direction.

The problem of aspirin resistance development depending on gender is controversial. According to a number of authors, women are more predisposed to the development of HRPR on the background of antiplatelet therapy [12]. Currently, there are no clear answers to this question, but it is assumed that there is a gender difference in the basic platelet reactivity, possibly due to differences in the functioning of neurohumoral mechanisms of vascular tone regulation and neurotransmitter synthesis.

CONCLUSION

The problem of antiplatelet drug's efficacy is widely and actively discussed in the scientific papers. The development of resistance to both ASA and P2Y12 inhibitors is quite prevalent. The factors that lead to the development of resistance can be divided into modifiable and nonmodifiable. Apparently, antiplatelet drugs resistance can also be considered in terms of the avoidable and unavoidable, which requires further study and systematization. The emergence of new methods for studying the mechanisms of HRPR development on the background of the use of antiplatelets may provide new tools in therapy personalization.

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CONFLICT OF INTERESTS

The authors declare no obvious and potential conflicts of interest related to the publication of this paper.

AUTHORS CONTRIBUTION

Kantemirova B.I. — design and writing of the manuscript, Zhidovinov A.A. — methodological and consulting help, Chernysheva E.N. — methodological and consulting help in writing the manuscript, Abdullaev M.A. — collection of reference literature, Orlova E.A. — structure of review, Sultanova O. — analysis of clinical material used in the paper.

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