Aspirin and Clopidogrel – Mechanism of Action, Interaction and Development of Resistance

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Summary. With low doses of aspirin clot formation on the plaques is delayed, but with high doses formation of atheromatous plaques is promoted, which can lead to thrombus formation. Antiplatelet effects of aspirin and clopidogrel are inhibited by other drugs that act through the same enzymes. Aspirin resistance is observed for from 5% to 45% or even 60% patients, but clopidogrel resistance is observed in average for 4–30%. Its mechanisms are multifactorial – the most common are genetic variations, accelerated platelet turnover, reduced aspirin bioavailability and alternative pathway of platelet activation and ineffective decomposition of clopidogrel to active metabolite. Knowledge about mechanisms of aspirin and clopidogrel action, interaction of drugs and development of resistance may help to understand and reduce ineffectiveness of these medications, that will help to reduce repeated cerebral and cardial infarctions in patients who use adequate antiplatelet therapy.

Keywords: antiplatelets, aspirin, clopidogrel, mechanism of action, interaction, resistance.

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Regardless of scientifically proven effectiveness of aspirin and clopidogrel in vascular event reduction, there are still noticed repeated cerebral and cardial infarctions in patients used adequate atiplatelets therapy. Knowledge about mechanisms of action, interaction of drugs and development of resistance may help to understand and reduce ineffectiveness of these medications.

ASPIRIN MECHANISM OF ACTION

The antithrombotic effect of aspirin (acetylsalicylic acid) first was revealed in 1945, and today it is the most used antiaggregant worldwide. Unfortunately, aspirin is a relatively weak antiaggregant because it interferes with only one mechanism leading to trombocyte activation. By arachidonic acid metabolizing enzyme cyclooxygenase (COX-1 and COX–2) inhibition aspirin reduces development of cyclic endoperoxide PGG_2 and prostaglandin PGH_2. In this way aspirin influences formation of thromboxane TXA_2 (platelet aggregatiom and vasoconstriction) and prostacyclin (antiaggregation and vasodilatation). Furthermore, action of aspirin to COX-1 in platelets is more forceful than to COX-2 in monocytes. As platelet cyclooxygenase is more sensitive than edothelial cyclooxygenase, thromboxane A_2 (TXA_2) synthesis is depressed faster and stronger than formation of prostacyclin. In such a way antiaggregant action of acetylsalicylic acid is provided (Figure 1).

When low acetylsalicylic acid dosages (75–320 mg per day) are used, a different influence to TXA_2 and prostacyclin formation is particularly well seen. Antiaggregant action maintains 8–12 days, what is a whole platelet life-

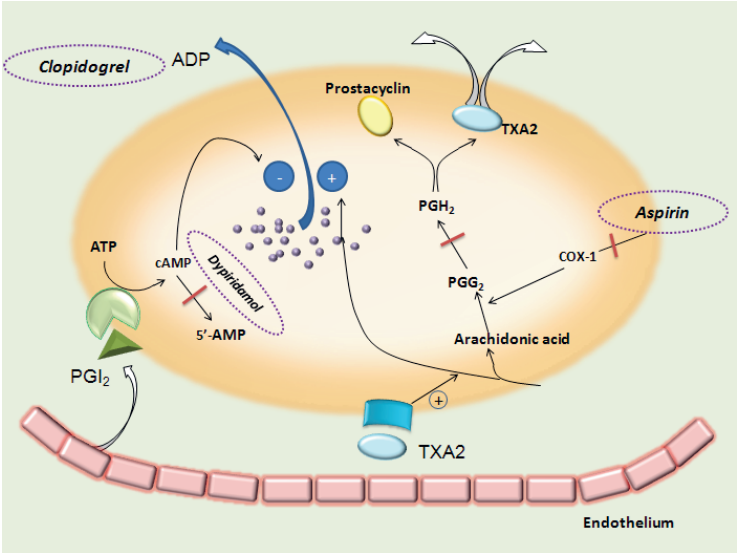

Figure 1. **Mechanism of antiaggregants action**
Modified from *McCann A. Antiplatelet therapy after coronarry occlusion. Australian Prescriber 2007; 30(4): 92–6.*

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span. Every day about 10% of circulating in blood platelets are replaced with new ones, produced by megakaryocytes in bone marrow. Low doses of acetylsalicylic acid are enough to suppress this function [1, 2]. On the contrary, blood vessel endothelial cyclooxygenase renews its function very fast, in few hours. So, after low dose aspirin usage TXA_2 decrease in blood is much longer than prostacyclin reduction. If dosage of aspirin is increased, the suppression of prostacyclin formation becomes apparent and the antiaggregant effect fades out. Bigger doses may induce formation of thrombocytic thrombus [1, 3].

Acetilsalicylic acid is rapidly absorbed and reaches maximal concentration after 30–40 minutes after ingestion, maximal antiplatelet effect is observed during 1 hour [2, 4]. In the liver acetilsalicylic acid is rapidly deacetylated and salicylate is formed. Salicylate has insignificant or no antiplatelet effect, but it has an anti-inflammatory action. Three hours after peroral ingestion, level of acetylsalicylate in plasma is very low. Due to the fact that acetilsalicylic acid inhibits cyclooxygenase of thrombocytes in some minutes, even the short time action of medication to platelets causes a full inactivation of this enzyme and supresses function of platelets. At intravenous application aspirin works even faster [1]. Due to the fact that aspirin in small doses influences platelet aggregation comparatively slowly, the first saturation dose 300–325 mg is recommended [3]. Usually, antithrombotic effect has upper limit at daily administration from 81 to 325 mg of aspirin, larger doses do not cause a stronger influence. Dose of aspirin smaller than 100 mg do not provide a fast antithrombotic effect, therefore as optimum dose for acute stroke patients is believed to be at least 160 mg per day [4, 5]. Only for those patients, who have a faster recovery of thrombocytes it is useful to increase the dosage. For patients with a high risk of cerebral infarction, having a critical carotid artery stenosis were tried aspirin dose up to 1300 mg per day but the results did not show any improvement comparing with those who obtained 325 mg per day. To obtain a full inhibition of the thrombocytes function, an inhibition of TAX_2 synthesis for 95% is necessary [1].

There is a perception that low doses of acetylsalicylic acid promote increase of diameter and number of atheromatous plaques, whereas higher doses (1.0 to 1.5 g per day) – reduce. This phenomenon is explained by the fact that high-doses of acetylsalicylic acid reduce the formation of leukotriene (the second metabolic pathway of arachidonic acid) and inhibit macrophages that host lipids and facilitate their accumulation in vascular walls [3]. Therefore, in deciding what dose of aspirin should be applied, it should be kept in mind that with low doses of aspirin clot formation on the plagues is delayed, but with high doses formation of atheromatous plaques is promoted, which in turn can lead to thrombus formation.

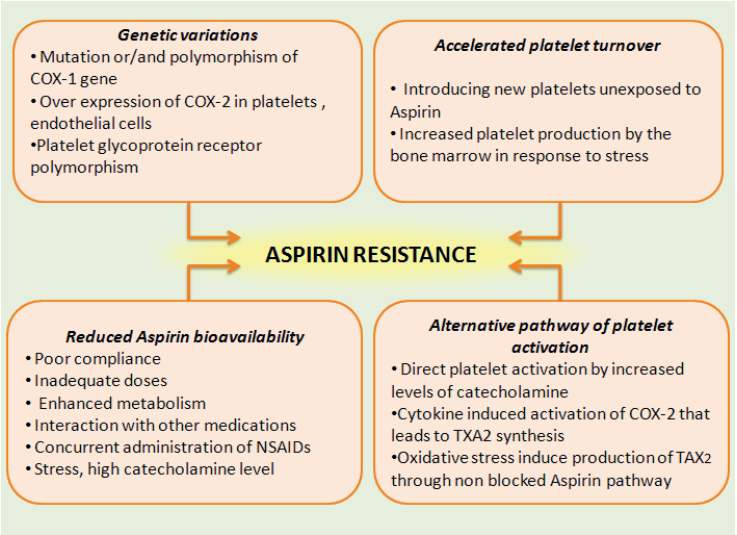

Figure 2. **Aspirin resistance development mechanisms**
Modified from *Smart S, Aragola S, Hutton P. Antiplatelet agents and anaesthesia. Continuing Education in Anaesthesia, Critical Care & Pain 2007; 7(5): 157–61.*

ASPIRIN RESISTANCE

The term "aspirin resistance" has been introduced to describe an inability of aspirin to inhibit platelet aggregation (biochemical aspirin resistance) and prevent from recurrent vascular event (treatment ineffectiveness). There is no single view of the prevalence of aspirin resistance. According to the literature aspirin resistance is observed for 5% to 45% [2] or 60% [58, 67] patients [5, 6].

The mechanism of development of resistance is multifactorial (Figure 2). Platelet aggregation is dependent on the patient's health status, time of day, physical activities, stress, cholesterol and blood glucose [2, 7]. Smoking also affects the aggregation and weakens the effectiveness of aspirin, similarly to non-steroidal anti-inflammatory drugs (NSAIDs) by blocking access of aspirin to COX-1 [5]. Ibuprofen is particularly prone to this effect, whereas diclofenac and rofecoxib cause a minimal or no impact at all on platelet aggregation, if they are administered concomitantly with aspirin [2]. In addition, aspirin at low doses (<100 mg) is a direct risk factor for the development of the resistance [5].

Mature platelets contain only COX-1 isoform, while the newly produced platelets, which represent 10% of circulating platelets in the blood volume, contain also a COX-2 isoform. At the time when increases the platelet count in the blood, the COX-2 produced thromboxane increases too. In such circumstances, the low or middle aspirin doses (81–325 mg) inadequately suppress platelet activity [2, 5].

Genetic effects on aspirin resistance can be explained by COX-1 gene, glycoprotein IIIa coding gene and PLA1/A2 glycoprotein Ia/IIa collagen receptor gene polymorphism. Patients with one or more of these gene polymorphisms may be resistant to aspirin antithrombotic ef-

fect. Platelets can be activated not only by TAX_2, but also by adenosine diphosphate, collagen, fibrin, and serotonin, which aspirin can not inactivate [2, 5].

Other aspirin resistance mechanisms are associated with inadequate inhibition of platelet activation caused by erythrocytes, prostaglandin-F_2 biosynthesis, increased platelet aggregation caused by catecholamines and a high platelet sensitivity to collagen [8].

Aspirin resistance treatment and prevention tactics is not yet clear to the end. It should be tried to eliminate all preventable causes of resistance – hypercholesterolemia, hyperglycemia, smoking, drugs known to cause interactions. High-doses of aspirin (>325 mg per day) promote an adequate response of platelets. Aspirin may be replaced by clopidogrel or a dual therapy with both agents implied, as they have a different mechanism of action [2].

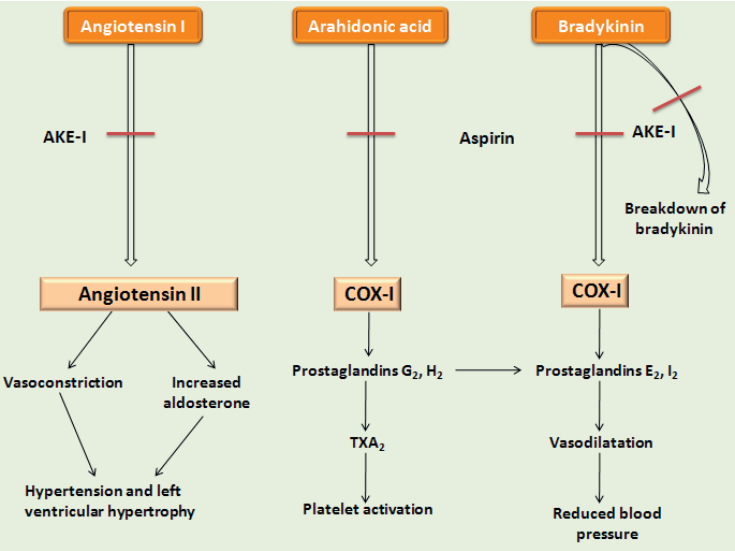

Figure 3. **Aspirin and ACE-I interaction**
Modified from *Peterson JG, Lauer MS. Using aspirin and ACE inhibitors in combination: Why the hullabaloo? Cleveland Clinic Journal of Medicine 2001; 68(6): 569–74.*

ASPIRIN INTERACTIONS WITH OTHER DRUGS

Antacids

Activity of aspirin is reduced by antacids. There is evidence that aspirin and ranitidine combination reduced platelet aggregation inhibition to the smaller extent than using aspirin alone. This phenomenon could be explained by a weaker absorption of aspirin if simultaneously ranitidine is used [9]. Oral antidiabetic agents in combination with aspirin may contribute to hypoglycemia [10].

Anti-inflammatory drugs

Administration of other anti-inflammatory drugs at the same time with aspirin increases the risk of adverse events – increasingly is irritated digestive tract, which can cause bleeding. Long-term used (more than 60 days per year) NSAIDs, particularly ibuprofen, celecoxib, rofecoxib, weaken anti thrombosis effect of small doses of aspirin (this effect is not observed if NSAIDs are short term administered), as a result risk of a cerebral infarction increases [11–14, 16]. Aspirin and ibuprofen interaction is associated with a competing drug binding to COX-1 enzyme, which binds aspirin irreversibly, so antithrombotic effect is durable. Ibuprofen binds reversibly to the enzyme and its effect on platelet function is transient.

Aspirin is quickly eliminated from the blood, so if aspirin intake in the body occurs during running ibuprofen, aspirin binding to COX-1 is smaller and weaker is antithrombotic effect [15, 16]. For this reason, using both drugs at the start aspirin should be taken, then after not less than eight hours – ibuprofen [16].

Other NSAIDs (diclofenac, flurbiprofen) do not hamper the effect of aspirin [12, 13].

ACE inhibitors

Related to aspirin and angiotensin converting enzyme inhibitors (ACE-Is), it is known that small doses of aspirin (<100 mg per day) cause less pronounced influence to ACE-Is than larger doses. This drug interaction occurs commonly in patients with coronary heart disease, hypertension and heart failure. However, so far no concrete information on interaction between these drugs exists. ACE-Is inhibit angiotensin-II production and hinder the breakdown of bradykinin. Amount of bradykinin increases and with aid of cyclooxygenase bradykinin stimulates synthesis of vasodilators prostaglandins. Aspirin, by blocking COX-1, inhibits not only formation of TXA_2 but also the production of prostaglandins, resulting in decreased ACE-I vasodilator effect (Figure 3) [17–20]. It should be borne in mind that these NSAIDs, which act on the COX-1, also reduce the effect of ACE-I, similarly to aspirin.

Mutual interaction is observed between aspirin and alcohol, and aspirin and anticoagulants in the form of higher risk of bleeding. Glucocorticoids in combination with aspirin promote the ulcerogenic action of drugs. Besides, acetylsalicylic acid weakens action of spironolactone and can cause toxicity of acetazolamide [10].

MECHANISMS OF ACTION OF CLOPIDOGREL

Clopidogrel is a derivative of thienopyridine, which has anti-platelet, expressed corona dilator, as well as anticoagulant properties. In contrast to acetylsalicylic acid it does not inhibit cyclooxygenase and does not affect the synthesis of prostaglandins. Antithrombotic effect is achieved as the hepatic cytochrome P450 isoenzyme interacts with

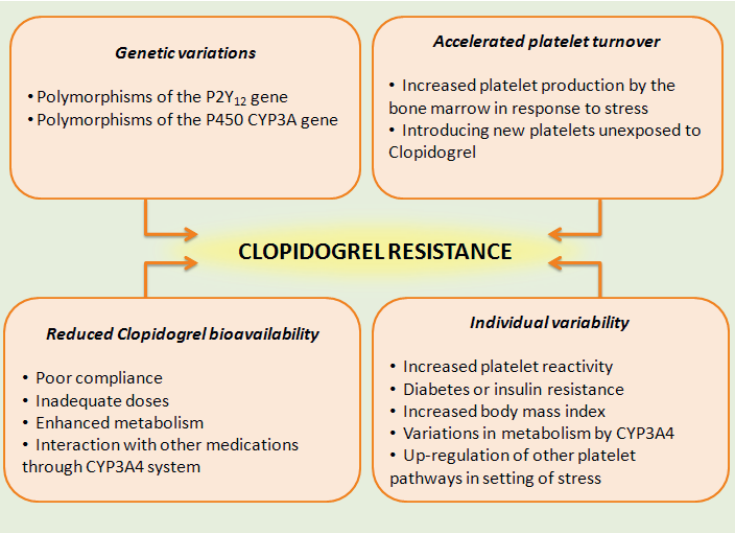

Figure 4. **Mechanisms of clopidogrel resistance**
Modified from *Smart S, Aragola S, Hutton P. Antiplatelet agents and anaesthesia. Continuing Education in Anaesthesia, Critical Care & Pain 2007; 7(5): 157–61.*

clopidogrel, in the result clopidogrel changes to its active metabolite SR 26334, which irreversibly binding to platelets receptors $P2Y_{12}$ inhibits stimulated by adenosine diphosphate (ADP) activation of platelets, as well as formation of $GP_{IIb\text{-}IIIa}$ complex, thereby preventing the fixation of fibrinogen on platelet surfaces and preventing the creation of fibrin bridges among platelets [21–25]. Recently it was shown that clopidogrel reduced activation and, consequently, a weak antithrombotic effect is related to the damage of CYP2C19*2 allele [1, 22, 26]. Patients with genetic polymorphism, for which weakness of function of enzyme CYP2C19 is observed, have a low level of active metabolite of clopidogrel in blood, and as a result the desired inhibition of platelets activity is not achieved in the time of clopidogrel application and a risk of repeated vascular events increases compared to patients who do not have the enzyme polymorphism [23, 25, 27–30].

Thienopyridines, by reducing binding of ADP and fibrinogen to platelet membrane, prevent platelet adhesion to artificial surfaces and brake deposition of platelets on atheromatous plaque. They reduce plasma fibrinogen levels and blood viscosity, increase the ability of red blood cells to deform, showing the rheological properties. Thienopyridines are active against a number of vasoconstrictors such as endothelin, TXA_2, probably by acting on vascular purinergic receptors [1].

Effect of clopidogrel is dose dependent. At administration of normal dose of medication (75 mg per day) beginning of an antithrombotic effect was observed after 2 hours and a maximum effect was reached after 3–5 days. In turn, increasing the dose to 300 mg of the preparation the maximum effect is achieved already after 6 hours. Therefore, to achieve a rapid and adequate antithrombotic effect, a first saturation dose 600 mg of clopidogrel is recommended, then continuing 75 mg per day at meal time or after that in the same time [1, 4].

Using clopidogrel, there is a risk of leucopenia (less frequently than using tyclopidin). It should be borne in mind also possible liver damages and symptoms, which indicate to them – dark urine, jaundice development, heaviness in the right subcostal region. For patients with liver or kidney disease liver function indicators should be monitored [10].

According to the literature, many patients have a higher residual activation of platelets after using of clopidogrel compared with administration of prasugrel. Platelet aggregation inhibition is closely related to a level of active metabolite, so the poor pharmacodynamic response to clopidogrel is more likely associated with a different absorption or metabolism of the preparation, or both of these factors.

Clopidogrel and prasugrel metabolic pathways have some differences. About 85% of the clopidogrel dose with esterases assistance is hydrolysed to inactive metabolite, which can not be converted into an active form. The remaining 15% of the clopidogrel dose are metabolized to the active metabolite, which is served by two cytochrome P450 (CYP) dependent pathways, in one of them CYP2A4/5, CYP2C9, CYP1A2 are involved and CYP2B6, VYP2C19 are involved in both ways. In essence, esterases way competes with the cytochrome path, and anything that hinders the formation of active metabolite can divert prometabolite (clopidogrel) to esterase path, resulting in formation of an inactive metabolite (Figure 4). Prasugrel, in turn is hydrolyzed by help of esterases to the active metabolite intermediate. Further this intermediate is oxidized to the active metabolite by help of one of the four enzymes (mainly by CYP2A4/5 or CYP2B6, to a smaller extent by VYP2C19 and CYP2C9). In this way prasugrel active metabolite can be formed by any of the four CYP enzymes and these enzymes are able to offset one another. Due to different metabolisms, factors which weaken CYP enzyme activity suppress formation of the clopidogrel active metabolite, but do not affect conversion of prasugrel to the active metabolite [2, 22, 23, 25, 27, 28, 31, 32].

This hypothesis is supported by the observation that at concomitant use of prasugrel and ketoconazol (potential CYP2A4/5 inhibitor) the active metabolite and pharmacodynamics of prasugrel were not affected, in contrast to clopidogrel, which was used together with ketoconazol – quantity of the active metabolite and pharmacodynamics of clopidogrel was decreased [22, 23, 31, 32].

A variable response to clopidogrel was observed. Patients, who obtain clopidogrel in their therapy, and experiencing a higher *ex vivo* platelet activity, are members of a high risk group of ischemic events. Different degrees of suppression of platelet aggregation with clopidogrel are due to a concomitant use of statins, calcium channel blockers (CaCBs), proton pump inhibitors (PPIs), H_2 receptor blockers, non-steroidal anti-inflammatory agents, coffee and smoking [21, 22, 33, 34].

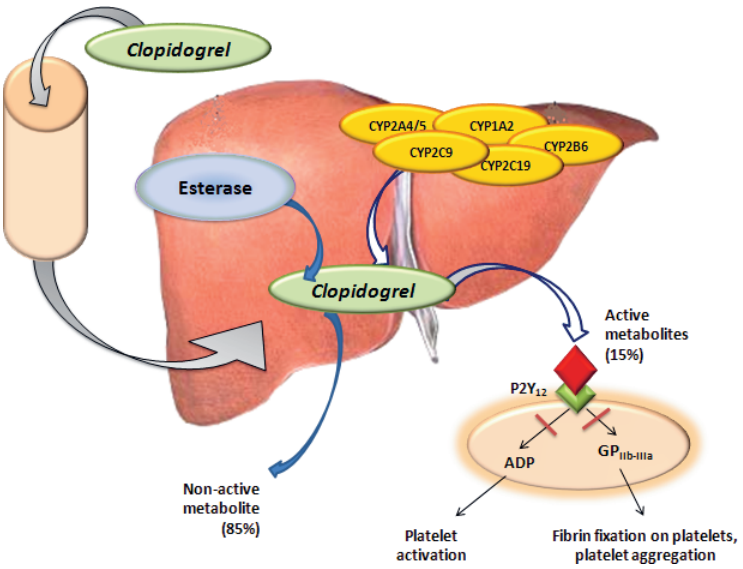

Figure 5. **Mechanisms of clopidogrel resistance**
Modified from *Tabassome S, Murielle MK, et al. Genetic determinants of response to Clopidogrel and cardiovascular events. The New England Journal of Medicine 2009; 360(4): 363–75.*

RESISTANCE TO CLOPIDOGREL

In the case of clopidogrel – resistance is observed in average for 4–30% [2, 35, 36] and for approximately 25% only partial sensitivity to this drug is observed [35]. The most common reason of resistance is an ineffective decomposition of clopidogrel to an active metabolite [37]. In the development of resistance a major role plays $P2Y_{12}$ gene polymorphism; abnormally increased signal transduction of receptors that promote platelet aggregation; high intracellular calcium levels; platelet membrane defect, inadequate dose in patients with elevated body mass index, and concomitant systemic diseases (Figure 5) [2, 5, 35, 38]. With insensitivity to clopidogrel patients are more frequently encountered after the age of 55, non-susceptive are also patients with diabetes. Diabetes often increases platelet activation and aggregation, which contributes to insulin resistance and increased $P2Y_{12}$ receptors activity [2, 38].

Increasing the dose of clopidogrel in the beginning prevents the creation of resistance during treatment [2, 5]. Thus, for example, the first dose of clopidogrel 600 mg on average more often than 300 mg dose causes a better suppression of aggregation within 24 hours. Doses larger than 600 mg are not more efficient because the clopidogrel absorption is limited [2, 39].

Options for prevention and treatment of clopidogrel resistance are not yet known to the end. It is necessary to eliminate removable reasons – to promote cooperation, prevent insulin resistance and drug interactions. Efficient can be doubling of the first dose of clopidogrel [2]. In a relatively small double-blind randomized trial (60 patients) after a percutaneous coronary intervention patients received the first clopidogrel dose 600 mg, after that in a 30 days time for a half of patients was administered 75 mg per day, for the other half – 150 mg. Platelet activity was statistically significantly lower in patients who received 150 mg dose [40]. In case of clopidogrel or aspirin resistance the problem can be solved using new $P2Y_{12}$ inhibitors, such as prasugrel or ticagrelor. These drugs adequately suppress the $P2Y_{12}$ dependent platelet function [37]. It is possible also to administrate GP IIb/IIIa receptor antagonists, because their mechanism of action is different [2].

CLOPIDOGREL IN INTERACTIONS WITH OTHER DRUGS

Statins

Clopidogrel and 3-hydroxy-3-metiglutaryl enzyme A reductase inhibitors (statins) are often administered concomitantly to patients with atherosclerosis. As is known, clopidogrel and some of the statin group of agents (atorvastatin, simvastatin, lovastatin, cerivastatin) are metabolized by the cytochrome enzyme CYP3A4, taking part also in metabolism of clopidogrel, but fluvastatin is metabolized by CYP2C9 [41, 42]. This led to a suggestion that combination of these preparations can interact with each other and suppress reduction of aggregation of platelets caused by clopidogrel. Large randomized prospective studies showed no statistically significant differences in terms of recovery, using CYP3A4 statins and non-CYP3A4 statins with clopidogrel [5, 41, 42]. Two *ex vivo* studies have demonstrated that atorvastatin inhibits antithrombotic activity of clopidogrel [43–45], however, in both these studies gold standard method – light transmission aggregometry was not used, by contrast, in all *ex vivo* studies, where this method was used, interaction between clopidogrel and statins was not confirmed and so the data are controversial [44, 46–51]. This means that the drug interaction is more likely to be *ex vivo* phenomenon and not clinically significant. There was found that fluvastatin and simvastatin suppress the antiaggregant effect of clopidogrel, which is not observed for atorvastatin, pravastatin and rosuvastatin [2, 52].

Literature provides an evidence that cytochrome CYP3A4 plays an important role in the metabolism of statins, clinically significantly interacting with other agents that are also metabolized through the CYP system (cyclosporine, erythromycin, ketoconazole) [48]. There is no evidence that pravastatin is metabolized through the CYP system [48].

Calcium channel blockers

Verapamil and diltiazem, as well as dihydropyrimidine CaCBs are moderate CYP3A inhibitors. As blood samples,

taken from patients, who were treated with clopidogrel were treated with CaCBs, the effect on platelet activity was not detected (this excludes a direct action of the drug) [24, 33, 34, 53, 54]. All this suggests that CaCBs weaken the functioning and effectiveness of clopidogrel.

Some CaCBs (verapamil, dilthiazem, nifedipine, barnidipine) have a pronounced blocking effect on drug transporting protein P-glycoprotein (Pgp), which provides clopidogrel absorption in the intestines. Statistically significant suppression of antithrombotic effect of clopidogrel was observed only in amlodipine users group [54]. Recently published results of the study, which included patients with acute myocardial infarction, are diagonally opposite the above mentioned beliefs. It was observed that recurrent myocardial infarction, stroke, and fatal outcome (for any reason, during the year) were equally frequent in both groups (who received or not received clopidogrel) [55] that is, suppressing action of CaCBs in relation to clopidogrel was not confirmed.

Proton pump inhibitors

In order to reduce the risk of gastrointestinal bleeding, caused by thienopyridins, often proton pump inhibitors (PPIs) are administrated. All PPIs are metabolized by the enzyme CYP2C19, but to a different extent, therefore not all PPIs suppress the clinical effect of clopidogrel [29, 56, 57]. In patients, who receive gastroprotection with omeprazole, a 4.3 fold weaker answer to clopidogrel is observed. This is due to enzyme CYP2C19 suppression caused by omeprazole (also by esomeprazole, lansoprazole and rabeprazole), resulting in fall of clopidogrel antithrombotic effect. CYP2C19 also acts as a primary enzyme, which provides a patient's body pharmacodynamic sensitivity to clopidogrel [25, 27, 34, 58]. In the case of esomeprazole there are data in the literature, which do not approve its interaction with clopidogrel [57]. In some studies suppressing activity of pantoprazole to CYP2C19 was not detected, that is pantoprazole does not affect the antiaggregant properties of clopidogrel [25, 29, 56, 57, 59]. Using prasugrel concomitantly with PPIs, a statistically significant weakness of its efficiency was observed only the first 30 minutes, and after 2, 6 and 24 hours the prasugrel effect is similar regardless of the PPI use. While during the first half of an hour activity of clopidogrel is the same for all patients, after 2, 6 and 24 hours antiaggregant effect of clopidogrel is statistically significantly inferior in patients receiving PPIs [60].

It was observed that 30% of white population, 40% of black population and more than 55% of East Asian population have a CYP2C19 gene polymorphism, which inhibits clopidogrel in pharmacodynamics and pharmacokinetics [29, 30]. If these patients are concomitantly administered by PPIs, risk of repeated vascular events and death increases many times [27–30]. In patients receiving PPIs, risk of repeated vascular events in year's time increases for more than 50%, compared with patients, who in addition to antiaggregants do not receive PPIs [25, 61]. Because of these facts, there are recommendations to administrate PPI together with clopidogrel only for patients at high risk (patients who receive a dual antiaggregant therapy; in history gastroduodenal bleeding or ulcer disease; while also receiving anticoagulant therapy) [27, 28].

Antacids

Solubility of prasugrel decreases as pH of gastric juice increases, suggesting that some concomitantly administered drugs can reduce prasugrel absorption [60]. Whenever required, administration of H_2 blockers (ranitidine, famotidine) may be considered, but, as known, these drugs are less efficient than PPIs [25, 27, 60]. It is also noted that both clopidogrel and prasugrel are well tolerated with and without ranitidine [60]. This suggests that ranitidine, similarly to other H_2 blockers, has a relatively weak effect on acidity of gastric juice. Nevertheless, scientists continue to investigate whether ranitidine acts on the $P2Y_{12}$ receptors, so that they can recommend the replacement of PPIs with ranitidine in patients receiving clopidogrel. So, data from investigation that was published in 2010 show that ranitidine, however, increases the ADP activation and suppresses $P2Y_{12}$ inhibition, which leads to platelet aggregation growth, as well as suppresses platelet adenyl cyclase level. In this way, ranitidine reduces the clinical effect of clopidogrel [60]. It should be noted that all of these studies had a very small number of respondents, thus the results obtained should be treated critically.

Based on the above information, it is preferably to administrate pantoprazole concomitantly with clopidogrel, as it is statistically significantly shown that these drugs do not affect each other's clinical effects [25, 29, 56, 58].

SUMMARY

With low doses of aspirin clot formation on the plagues is delayed, but with high doses formation of atheromatous plaques is promoted, which can lead to thrombus formation. Antiplatelet effects of aspirin and clopidogrel are inhibited by other drugs that act through the same enzymes. Aspirin resistance is observed for from 5% to 45% or even 60% patients, but clopidogrel resistance is observed in average for 4–30%. Its mechanisms are multifactorial – the most common are genetic variations, accelerated platelet turnover, reduced aspirin bioavailability and alternative pathway of platelet activation and ineffective decomposition of clopidogrel to active metabolite. Knowledge about mechanisms of aspirin and clopidogrel action, interaction of drugs and development of resistance may help to understand and reduce ineffectiveness of these medications, that will help to reduce repeated cerebral and cardial infarctions in patients who use adequate antiplatelets therapy.

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ASPIRINAS IR KLOPIDOGRELIS – VEIKIMO MECHANIZMAI, SĄVEIKA IR REZISTENTIŠKUMO VYSTYMASIS

Santrauka

Skiriant mažas aspirino dozes, krešėjimo procesai ant plokštelių paviršiaus sulėtėja, tačiau taikant dideles dozes skatinama formuotis ateromatozinėms plokštelėms, galinčioms sukelti trombo susidarymą. Aspirino ir klopidogrelio antitrombocitinį poveikį slopina kiti vaistai, veikiantys per tas pačias fermentines sistemas. Rezistentiškumas aspirinui stebimas nuo 5 % iki 45 % ar net 60 % pacientų, o rezistentiškumas klopidogreliui pasitaiko 4–30 % pacientų. Rezistentiškumo mechanizmai yra įvairūs – dažniausiai tai genetinės variacijos, pagreitėjusi trombocitų kaita, sumažėjęs aspirino bioprieinamumas, alternatyvūs trombocitų aktyvacijos keliai ir neefektyvus klopidogrelio skilimas į aktyvius metabolitus. Žinios apie aspirino ir klopidogrelio veikimo mechanizmus, vaistų tarpusavio sąveiką ir rezistentiškumo vystymąsi gali padėti suprasti ir suretinti šių vaistų neveiksmingumą. Tai padės sumažinti pakartotinių smegenų ir širdies infarktų riziką adekvatų gydymą antiagregantais vartojantiems pacientams.

Raktažodžiai: antiagregantai, aspirinas, klopidogrelis, veikimo mechanizmas, sąveika, rezistentiškumas.