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Comparison of pharmacodynamic properties of three different aspirin formualtions in the patients with stable coronary disease

Poređenje farmakodinamskih osobina tri različita preparata aspirina kod bolesnika sa stabilnom koronarnom bolešću

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Abstract

Background/Aim. The platelet aggregation, as a laboratory test for assessment of platelet function, is very efficient for optimal antiplatelet treatment and also to identify individuals who have suboptimal response to antiplatelet drugs, such as aspirin and clopidogrel. The aim of this study was to determine the level of inhibition of platelet aggregation using impedance aggregometry in the patients receiving different preparations of acetylsalicylic acid (ASA) in a dose of 100 mg per day. **Methods.** The examination included 215 patients (110 men and 105 women), treated with one of three different ASA preparations after acute myocardial infarction, as a single therapy or with clopidogrel. Among them, 89 patients were on Aspirin protect® (Bayer, Germany) – Group 1 and 66 patients were on Cardiopirin® (GL Pharma GMBH, Austria) – Group 2, while 60 patients were taking Andol® (Pliva, Croatia) – Group 3. The groups were equal in the presence of factors that can influence platelet aggregation (age, gender, smoking, diabetes, taking other drugs). The platelet function was measured using the impedance aggregometer Multiplate (Multiplate Platelet Function Analyzer, Roche) in the blood samples with heparin for the platelet aggregation activated by the arachidonic acid (ASPI) and by thrombin (TRAP) tests [the area under the aggregation curve (AUC) was used to express the aggregation response over the measured time (AU*min)]. **Results.** Efficacy of ASA preparations showed statistically significant differences among the three investigated groups ($\chi_{KW}^2 = 46.279$; $p < 0.001$), and it was also observed separately in the patients undergoing single therapy ($\chi_{KW}^2 = 26.344$; $p < 0.001$) and dual therapy ($\chi_{KW}^2 = 23.498$; $p < 0.001$). It was found that the patients who were taking Aspirin protect® obtained significantly better antiplatelet efficiency compared to the patients receiving Cardiopirin® ($Z = 5.472$; $p < 0.001$) and Andol® ($Z = 5.387$; $p = 0.022$). There is reduced efficiency of all ASA preparations in smokers, while patients receiving Aspirin protect® were 10.5 times more likely to be responders. **Conclusion.** Different ASA preparations observed in this study showed different efficiency on the platelet function as measured by the method of impedance aggregometry.

Key words:
platelet aggregation; aggregation inhibitors; aspirin; clopidogrel; acute coronary syndrome; treatment outcome.

Apstrakt

Uvod/Cilj. Agregacija trombocita, kao laboratorijski test za procenu funkcije trombocita, je od posebnog značaja za optimalno vođenje antitrombocitne terapije i izdvajanje bolesnika koji pokazuju suboptimalni odgovor na primenu antitrombocitnih lekova, kao što su aspirin i klopidogrel. Cilj rada bio je odrediti stepen inhibicije agregacije trombocita metodom impedantne agregometrije kod bolesnika koji su uzimali različite preparate acetilsalicilne kiseline (ASA) u dozi od 100 mg dnevno. **Metode.** Ispitivanjem je obuhvaćeno 215 bolesnika (110 muškaraca i 105 žena), koji su nakon infarkta miokarda sa naknadnom revaskularizacijom uzimali jedan od tri različita preparata ASA, pojedinačno ili u kombinaciji sa klopidogrelom. Od ukupnog broja, 89 bolesnika je uzimaloAspirin protect® (Bayer, Nemačka) – Grupa 1, Cardiopirin® (GL Pharma GMBH, Austrija) je uzimalo 66 bolesnika– Grupa 2, dok je 60 bolesnika primalo Andol® (Pliva, Hrvatska) – Grupa 3. Grupe su bile jednake u zastupljenosti faktora koji mogu biti od uticaja na agregaciju trombocita (starost, pol, pušenje, diabetes, uzimanje drugih lekova). Funkcija trombocita merena je na impedantnom agregometru Multiplate (Multiplate Platelet Function Analyzer, Roche) iz uzoraka krvi sa heparinom, korišćenjem

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agregacije trombocita aktiviranih arohidonskom kiselinom (ASPI) i trombinom (TRAP) [rezultati su bili izraženi kroz površinu ispod agregacione krivulje u periodu ispitivanja (AU*min)]. **Rezultati.** Ustanovljena je statistički značajna razlika u efikasnosti različitih preparata ASA ($\chi_{KW}^2 = 46{,}279$; $p < 0{,}001$), kako kod bolesnika koji su na pojedinačnoj ($\chi_{KW}^2 = 26{,}344$; $p < 0{,}001$), tako i onih na dvojnoj terapiji ($\chi_{KW}^2 = 23{,}498$; $p < 0{,}001$). Bolesnici koji su uzimali Aspirin protect® su imali značajno bolju antiagregacionu efikasnost leka u poređenju sa bolesnicima koji su uzimali Cardiopirin® ($Z = 5{,}472$; $p < 0{,}001$) i Andol® ($Z = 5{,}387$; $p = 0{,}022$). Postojao je smanjeni efekat svih preparata ASA kod pušača, dok su bolesnici koji su uzimali Aspirin protect® imali 10,5 puta veću verovatnoću da budu responderi. **Zaključak.** Različiti preparati acetilsalicilne kiseline posmatrani u ovom ispitivanju pokazuju laboratorijski značajno različitu efikasnost na funkciju trombocita merenu metodom impedantne agregometrije.

Ključne reči:
trombociti, agregacija; antiagregaciona sredstva; aspirin; klopidogrel; akutni koronarni sindrom; lečenje, ishod.

Introduction

Antiplatelet therapy shows a significant benefit in the treatment of acute coronary syndrome (ACS). For over 100 years acetylsalicylic acid (ASA) has been used as an anti-inflammatory and antipyretic drug, but since the end of 1960s it has been known that ASA also reaches its positive cardiovascular effects in the inhibition of thromboxane A_2 (TxA_2) by acting on the enzymes cyclooxygenase-1 (COX-1) and cydooxygenase-2 (COX-2) [1, 2]. The effect of ASA on COX-1 is irreversible and lasts for the life of the platelets, depending on the production of new platelets which will recover COX-1 activity at a rate of about 10% per day in healthy people. Low doses of ASA are sufficient to suppress more than 95% of TXA_2 synthesis by COX-1, which leads to inhibition of platelet aggregation. However, platelets affected with ASA may still aggregate in the presence of potent platelet agonists such as collagen and thrombin. Higher doses of ASA can inhibit COX-2 mediated synthesis of prostacyclin in endothelial cells, but they retain the ability to regenerate the production of prostacyclin a few hours after ingestion of ASA due to the ability of cells to synthesize the core protein [2, 3].

Despite its significant antiplatelet effect, ASA is not always able to prevent all cardiovascular events. This is far from surprising when considering the complexity of arterial thrombosis and specific platelet physiology [4]. This lack of therapy success was the reason for introduction various diagnostic tests with the intent of guiding and optimizing the clinical treatment of patients. Such tests have resulted in the generation of clinical data that suggest suboptimal response to antiplatelet agents such as ASA or clopidogrel, which is called "resistance" [5–7].

The definition of ASA resistance is quite variable in the literature and has been described as the occurrence of thromboembolic events despite ASA intake, insufficient pharmacological inhibition of COX-1-derived TXA_2 formation with subsequent insufficient inhibition of platelet function, or the inability of the drug to cause prolongation of bleeding time [7–9]. It should be noted that most experts prefer to use the term "variable response" instead of ASA resistance, which indicates that the response to ASA differs among some patients, and may be attributed to various individual-, drug- or disease-related reasons or mechanisms [5, 7, 9]. Several mechanisms were identified to explain the incidence of variable response to ASA: non-compliance, age, sex, smoking, possible drug interactions (nonsteroidal anti-inflammatory drugs – NSAIDs, inhibitors of proton pump), inadequate dosing, alternative pathways of platelet activation, altered platelet response to ASA under some conditions/surgical procedures (e.g., coronary artery bypass grafting – CABG), genetic variations of COX-1 gene or platelet receptors, pre-treatment platelet reactivity and pre-existing clinical conditions (diabetes mellitus, renal failuire, essential thrombocythaemia) [10–15].

The possibility of monitoring the platelet response to the ASA therapy can have a great impact on the management of therapy and significantly reduce the incidence of morbidity and mortality. The most important thing is to distinguish patients who do not receive the necessary protection with ASA, but also to determine possible causes of treatment failure [16, 17]. The most clinically meaningful measure of the platelet-inhibitory effects of ASA is the level of serum thromboxane B_2 (TxB_2) which reflects thromboxane $A_2$$TxA_2$) formation by platelets [18]. Other methods that are efficient in optimal management of antiplatelet therapy and identification of the patients who have a suboptimal response to antiplatelet drugs are light transmission and impedance aggregometry, thromboelastography, bleeding time assay and flow cytometric analysis [19–21].

The aim of this investigation was to test the platelet function by the method of impedance aggregometry in the patients receiving various preparations of ASA in order to determine whether the type of ASA preparation affects the degree of inhibition of platelet aggregation and thus affects the degree of variable response to ASA.

Methods

The study included 215 patients who received a single (ASA) or dual (ASA + clopidogrel) antiplatelet therapy after acute myocardial infarction with revascularization. These patients were not at the same time on NSAIDs, and the patients were not with established thrombocytopenia or thrombocytosis (platelet count was 150–300 x 10^9/L). All patients had normal renal function (creatinine clearance greater than 60 mL /min). The patients were taking 3 types of ASA preparations in the from of tablets in a single dose of 100 mg daily at least for 2 months, but the longest for 6 months: Aspirin protect® (Bayer, Germany) – Group 1, Cardiopirin® (GL Pharma GMBH, Austria) – Group 2 and Andol® (Pliva, Croatia) – Group 3. The groups were equal in the presence of

factors that can influence the platelet aggregation (age, gender, smoking, diabetes, taking other drugs).

The platelet function was measured using impedance aggregometer Multiplate (Multiplate Platelet Function Analyzer, Roche) in the blood samples of 4 mL with lithium heparin as antucoagulant (VenoSafe, Terumo) for the platelet aggregation activated by arachidanic acid (ASPI test) and by thrombin activator peptide (TRAP test). The blood samples were taken 4 hours after taking ASA. The procedure implied adding 300 ml of the heparinized blood and 300 mL of the saline solution into the test cell. After incubation at 37°C for 3 minutes, 20 mL of the selected agonist was added, so the final concentration of arachidonic acid (AA) of 0.5 mM (ASPI test) and TRAP of 3.2 uM (TRAP test) was achieved. A blood sample containing added agonist was automatically stirred (800 U/min) using a magnetic stirrer coated with poly-tetra-fluoro-ethylene (PTFE). The activated platelets adhere to the electrode and increase the electrical impedance between them, which was registered within 6 minutes, and the increase in impedance was converted into arbitrary units aggregation (aggregation arbitary units – AU). The area under the aggregation curve (AUC) was used to express the aggregation response over the measured time (AU*min). According to the manufacturer, the reference values were 923–1509 AU∗ min for TRAP test and 790–1410 AU∗ min for ASPI test. If ASPI was < 400 AU∗ min, the patient was assigned as ASA-responder.

Further, we considered the risk factors that may affect the efficacy of ASA preparations, such as smoking, gender, age, diabetes mellitus or taking other drugs [anticoagulant agents, proton pump inhibitors (PPIs) and β- blockers].

Statistical analysis was performed using the Statistical Package for Social Science (SPSS Software GmbH, Germany), version 20.0. The results were presented in tables and graphs, using the mean values and standard deviations (SD). The efficacy of ASA preparations among the groups was compared using the χ^2-test, ANOVA, Kruskal-Wallis test and Mann Whiney U test. Logistic regression analysis was used to determine the predictive factors in the assessment of drugs efficacy. Statistical significance was determined at the level of $p < 0.05$.

Results

From the total of 215 patients in this study, there were 110 men (110/215 or 51.2%) and 105 women (105/215 or 48.80%). The average age of patients in the study was 55.8 ± 11.2 years; the youngest patient was 24 and the oldest one was 80 years of age. There was no statistically significant difference in the age structure of patients by gender ($t = 1.163$; $p = 0.046$).

All the patients were divided into three groups according to the type of the applied ASA preparation: Group 1 (Aspirin protect®) – 89 (41.4%) patients, Group 2 (Cardiopirin®) – 66 (30.7%) patients, Group 3 (Andol®) – 60 (27.9%) patients. Most of the patients were on a single therapy – 121 (56.3%) patients, 55 (45.4%) of them were in the Group 1, 33 (27,3%) patients in the Group 2 and 33 (27.3%) patients were in the Group 3. On the other hand, 94 patients were at dual therapy, 34 (36.2%) of them in the Group 1, 33 (35.1%) patients were in the Group 2 and 27 (28.7%) patients were in the Group 3.

Table 1 shows the general characteristics of the patients in relation to the type of ASA preparation.

Table 1

General characteristics of the patients

Patients characteristics	Group 1	Group 2	Group 3	χ^2/F*	*p*
	n (%)	n (%)	n (%)		
Sex					
m	45 (50.6)	34 (51.1)	31 (51.7)		
f	44 (49.4)	32 (48.5)	29 (48.3)	0.022	0.989
Age (years), mean ± SD	56.09 ± 11.31	54.29 ± 11.96	57.10 ± 10.48	1.046*	0.353
Diabetes mellitus					
yes	21 (23.6)	16 (24.2)	18 (30.0)		
no	68 (76.4)	50 (75.8)	42 (60.0)	0.862	0.650
Smoking					
yes	33 (37.1)	29 (43.9)	34 (56.7)		
no	56 (62.9)	37 (56.1)	26 (43.3)	5.584	0.061
Anticoagulants					
yes	35 (39.3)	16 (24.2)	19 (31.7)		
no	54 (60.7)	50 (75.8)	41 (68.3)	3.957	0.138
Beta blockers					
yes	41 (46.1)	34 (51.5)	29 (48.3)		
no	48 (53.9)	32 (48.5)	31 (51.7)	0.450	0.798
Proton pump inhibitors					
yes	26 (29.2)	19 (28.8)	18 (30.0)		
no	63 (70.8)	47 (71.2)	42 (70.0)	0.023	0.989

χ^2-Chi sqare test; F-ANOVA – analysis of variance; SD – standard deviation.
Group 1 – Aspirin® protect (Bayer, Germany) á 100 mg; Group 2 – Cardiopirin® (GL Pharma GMBH, Austria) á 100 mg; Group 3 – Andol® (Pliva, Croatia) á 100 mg.

Table 2

Assessment of efficiency of acetylsalicylic acid (ASA) preparations in all groups

Therapy	test	Group 1 (n = 89) mean ± SD	Group 2 (n = 66) mean ± SD	Group 3 (n = 60) mean ± SD	F/$^{*}\chi_{KW}^2$	*p*
Total	TRAP	1166.82 ± 207.23	1186.32 ± 248.78	1125.32 ± 210.63	1.238	0.292
(n = 210)	ASPI	301.93 ± 122.98	521.29 ± 270.71	459.60 ± 185.89	46.279*	< 0.001
Single therapy	TRAP	1184.85 ± 206.26	1152.73 ± 229.19	1131.97 ± 190.14	0.704	0.496
(n = 121)	ASPI	319.84 ± 121.98	576.76 ± 290.15	469.06 ± 200.22	26.344*	< 0.001
Dual therapy	TRAP	1137.65 ± 208.349	1219.91 ± 266.19	1117.18 ± 236.75	1.630	0.202
(n = 94)	ASPI	272.97 ± 120.78	465.81 ± 241.50	448.04 ± 169.79	23.498*	< 0.001

F-ANOVA – analysis of variance; χ_{KW}^2 – Kruskal-Wallis Test; SD – standard deviation.
Group 1 – Aspirin protect® (Bayer, Germany) á 100 mg; Group 2 – Cardiopirin® (GL Pharma GMBH, Austria) á 100 mg; Group 3 – Andol® (Pliva, Croatia) á 100 mg; TRAP test – platelet aggregation activated by thrombin receptor activator peptide; ASPI test – platelet aggregation activated by archidonic acid.

The sex and age distribution did not differ significantly by the group. Also, the groups were homogenous according to the smoking status and the presence of diabetes. The differences did not exist in relation to the use of anticoagulants, beta-blockers and PPIs.

The general assessment of the efficacy of ASA preparations and a comparison between the groups regardless of the type of antiplatelet therapy (single, dual) is shown in Table 2.

The TRAP values did not differ significantly among the groups (F = 1.238; $p = 0.292$), in the patients on single therapy (F = 0.371; $p = 0.069$) as well as on a dual therapy (F = 1.299; $p = 0.280$), which indicated the similar basic function of platelets in all the patients.

The efficacy of ASA preparations showed statistically significant differences among the three investigated groups ($\chi_{KW}^2 = 46.279$; $p < 0.001$), and it was also observed separately in the patients undergoing single therapy ($\chi_{KW}^2 = 26.344$; $p < 0.001$) and dual therapy ($\chi_{KW}^2 = 23.498$; $p < 0.001$). Examining the efficacy of ASA in all patients, it was found that the patients who were taking Aspirin protect® obtained significantly better efficiency compared to the patients receiving Cardiopirin® (Z = 5.472; $p < 0.001$) and Andol® (Z = 5.387; $p = 0.022$). Significantly better efficacy of Aspirin protect® is also determined in both groups of patients on the individual and dual antiaggregation therapy.

Logistic regression model of independent factors for the assessment of effectiveness of ASA preparations for all patients in this study is shown in Table 3, where all patients are divided into responders (ASPI ≤ 400 AU*min) and non-responders (ASPI > 400 AU*min). This model included the following variables: age, diabetes, smoking, anticoagulants, beta blockers, PPIs and the type of applied ASA preparation.

The whole model was highly significant [χ^2 (df = 9, N = 215) = 112.658, $p < 0.001$)] and explained between 40.8% and 54.9% of the variance of efficiency of all ASA preparations according to the ASPI test. The factors that gave statistically significant contribution to the model were smoking [odds ratio (OR) = 0.108; $p < 0.001$) and the use of Aspirin protect® (OR = 10.538; $p < 0.001$)]. In the non-smokers the probability for values of ASPI < 400 AU*min increased for 89.2% compared to the smokers, while the patients receiving Aspirin protect® were 10.5 times more likely to have a value of ASPI < 400 AU*min.

Table 3

Logistic regression model of independent factors for assessing the efficiency of acetylsalicylic acid (ASA) for all the patients according to ASPI test

Factors	OR	95% CI	*p*
Gender	0.658	0.308–1.407	0.281
Age	1.024	0.990–1.059	0.174
Diabetes	0.868	0.315–2.391	0.784
Smoking	0.108	0.040–0.293	< 0.001
Anticoagulants	1.794	0.677–4.753	0.240
Beta blockers	0.812	0.388–1.701	0.581
PPIs	0.398	0.153–1.039	0.060
Aspirin protect®	10.538	3.893–28.526	< 0.001
Cardiopirin®	0.902	0.358–2.271	0.827
Andol®	1.109	0.440–2.792	0.832

OR – odds ratio; PPIs-proton pump inhibitors;
CI – confidence interval; ASPI test – platelet aggregation activated by arachidonic acid.

Table 4 shows the three logistic regression models of independent factors for the assessment of effectiveness of three different ASA preparations, where all patients were also divided into responders (ASPI ≤ 400 AU*min) and non-responders (ASPI > 400 AU*min). The models included the following variables: age, diabetes, smoking, anticoagulants, beta blockers and PPIs.

The first model included the patients from the Group 1. The whole model was highly significant χ^2 (df = 7, N = 89) = 17.299, $p = 0.016$) and explained between 17.7% and 29% of the variance of efficiency of Aspirin protect®. However, none of the variables was marked as statistically significant.

The second model included the patients from the Group 2. The model was highly statistically significant [χ^2 (df = 7, N = 66) = 51.939, $p < 0.001$] and generally explained between 54.5% and 73.2% of the variance of the efficiency of Cardiopirin®. A statistical significant contribution to the model had the following factors: gender (OR = 0.093; $p = 0.020$) and smoking (OR = 0.003; $p < 0.001$).

The third model consisted of patients from the Group 3. The model was highly statistically significant [χ^2 (df = 7, N = 60) = 43.199, $p < 0.001$] and generally explained between 51,3% and 69.4% of the variance of efficiency of Andol®. However, none of the factors was statistically significant.

Table 4

Logistic regression model of independent factors for assessing the efficiency of Aspirin protect®, Cardiopirin® and Andol® according to ASPI test

Factors	OR	95% CI	*p*
Model 1 (Aspirin protect®)			
gender	0.888	0.228–3.458	0.864
age	1.054	0.996–1.115	0.067
diabetes	0.821	0.155–4.343	0.817
smoking	0.498	0.106–2.346	0.378
anticoagulants	7.377	0.834–65.261	0.072
beta blockers	0.709	0.191–2.628	0.607
PPIs	0.622	0.191–2.628	0.592
Model 2 (Cardiopirin®)			
gender	0.093	0.012–0.692	0.020
age	1.048	0.970–1.132	0.238
diabetes	0.157	0.004–6.872	0.337
smoking	0.003	0.000–0.069	<0.001
anticoagulants	0.179	0.024–1.348	0.095
beta blockers	1.476	0.259–8.400	0.661
PPIs	0.203	0.021–1.918	0.164
Model 3 (Andol®)			
gender	0.664	0.104–4.224	0.664
age	0.911	0.822–1.010	0.077
diabetes	0.139	0.006–3.305	0.222

OR – odds ratio; PPIs-proton pump inhibitors; CI – confidence interval; ASPI test – platelet aggregation activated by arachidonic acid.

Discussion

The antiplatelet therapy cannot provide the prevention of all cardiovascular events, but the inhibitory effect on the platelet aggregation significantly decreases the cardiovascular morbidity and mortality. According to data from the American Heart Association (AHA) and the European Society of Cardiology (ESC), the therapy with ASA in a dose of 100 mg daily has significant therapeutic effects in the patients with moderate cardiovascular risk. In the patients with primary coronary intervention (PCI), with or without stenting, it is recommended to use clopidogrel (75 mg per day) in combination with ASA in an initial dose of 300 mg, and subsequently to reduce the dose to 75–100 mg daily [22]. Also, the recommended initial treatment in the patients with acute ischemic attack, who do not have thrombolytic therapy, is ASA in a dose of 150 to 325 mg and in the further therapy, it is recommended to use ASA in a dose of 100 mg daily with clopidogrel, 75 mg daily [23, 24].

The potential relation between the low response to antiplatelet therapy and clinical outcome has not yet been fully explained, mainly due to the fact that there is no universally accepted definition of resistance. The term platelet resistance should not be used lightly, because it can have a bad effect if it is not interpreted correctly. Misidentified, it can produce increased risk of thrombosis if the treatment is discontinued. On the other hand, there is a risk of hemorrhage if a dose of antiplatelet drug is wrongly increased. Some studies showed the inconsistent levels of resistence to ASA. Data range from 1.4%–9.8% [25] to 55% [26], but the majority of studies presented the incidence of 15%–33% of individuals with bad response to ASA [27–31]. The rates are slightly higher in the patients with a stroke. Recent studies have shown that nonresponsiveness to the antiplatelet drugs is a risk factor for thromboembolic events (stroke, myocardial infarction, vascular death). Škorić et al. [32] concluded in their study that initial patency of the infarct-related artery in the patients with the acute ST elevation myocardial infarction is related to the platelet response to aspirin. Also, Gum et al. [33] documented in their investigation a greater than threefold increase in the risk of major adverse events associated with the ASA resistence. A recent meta-analysis of 20 studies included more than 2,900 patients and reported that the patients with the lower response to ASA had a significantly increased risk of having a cardiovascular event [34]. Given these data and conclusions, it is clear that measuring the antiplatelet effect of ASA is of a great relevance.

Nowadays, there is a large number of commercial tests available to monitor the effects of ASA, in order to identify the patients who are at substantial risk for adverse events while they are on therapy. Recent studies have shown that the impedance aggregometry can be reliably used to assess the effect of ASA therapy, because it shows a high degree of sensitivity and good correlation with other testing methods [2, 16]. The variability of response to a given ASA is not a surprise, given that the environment, genetics, and disease can affect the drug's disposition. The most important factors that influence the effectiveness of ASA are the age, gender, the

presence of diabetes, smoking and concomitant therapies, such as the PPIs, antihypertensive drugs and the anticoagulant drugs. It is known that diabetes mellitus is associated with underlying platelet over-reactivity, which may attenuate the response to aspirin [10], tobacco use increases platelet activation and accentuates platelet thrombosis [8], while concomitant administration of PPIs reduces the effect of ASA due to the weaker absorption enhanced by esterases of gastrointestinal mucosa [11]. Our investigation showed that the statistically significant factors for the efficiency of ASA are smoking and the type of ASA preparation, where we can see that the patients receiving Aspirin protect® were 10.5 times more likely to be responders in the ASPI test.

There are not published data yet whether the selection of ASA preparation can affect the therapy itself and whether the kind of ASA preparations taken in the same dosage and in the same way can affect its effectiveness. This is important especially due to the fact that many authors do not recommend increasing the dose of ASA to achieve and maintain an effective level of antiplatelet activity because of the possibility of increased bleeding, especially in the patients with a stroke. Therefore, there are important implications for being able to optimize the efficiacy and safety of ASA preparations.

Our investigation showed that the 3 ASA preparations, which are available in our market, demonstrate their effectiveness comparable to the data in the literature. However, the effectiveness of ASA preparations, which is measured in this investigation by the method of impedance aggregometry, showed a statistically significant difference. In general, regardless whether patients were taking just ASA or ASA with clopidogrel, Aspirin protect® showed significantly higher efficiency compared to Cardiopirin® and Andol® ($\chi_{KW}^2 = 46.279$; $p < 0.001$). The same relation exists in the group of patients on a single therapy ($\chi_{KW}^2 = 26.344$; $p < 0.001$), as well as in the group of patients who had the dual therapy ($\chi_{KW}^2 = 23.498$; $p < 0.001$). Comparing the factors that may influence the efficiency of different ASA preparations, we found that none of the evaluated factors were statistically significant for the effectiveness of Aspirin protect® and Andol®, while gender and smoking were significant for Cardiopirin®. It is known that hormonal changes in women can enhance the platelet activation [8] and ASA bioinactivation by the liver may be slower in older patients than in younger ones, but it is important to point out that the gender was not showed to be an important factor for the efficacy of all ASA preparations, although, thus increasing the bioavailability in this group [35].

The results of our research confirm our assumption that together with all the factors, we know that can influence the effectiveness of ASA, selection of ASA preparation can also impact on the outcome of therapy. Although we can't clinically prove that the type of ASA preparations is of an importance for the effectiveness of antiplatelet therapy, it seems reasonable that the laboratory assessment of the efficiency of ASA preparations is taken into consideration as one of the criteria, and a type of ASA preparation as one of the factors which affect the anti-platelet effect of ASA.

Conclusion

Various preparations of acetylsalicylic acid examined in this investigation showed significantly different laboratory efficiency on the platelet function as measured by the method of impedance aggregometry.

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