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Enhanced antiplatelet effect of enteric--coated acetylsalicylic acid in co-administration with pantoprazole

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ABSTRACT

Background. Proton pump inhibitors (PPI) are recommended for patients receiving antiplatelet therapy. Several studies have revealed that PPI may attenuate the antiplatelet effect of ASA. However, our pilot study has indicated a positive interaction between pantoprazole and enteric-coated aspirin. The aim of the current study was to confirm that pantoprazole enhances the antiplatelet effect of enteric-coated aspirin in patients with acute coronary syndrome (ACS) treated with dual antiplatelet therapy. Moreover, the influence of CYP2C19 polymorphism on the antiplatelet effect of aspirin was assessed.

Material and methods. Ninety three consecutive ACS patients were prospectively enrolled in a randomized, crossover, open-labeled study. Forty four patients were given orally 40 mg of pantoprazole for the initial four days while the remaining forty nine were treated with pantoprazole from the 5th to the 8th day of hospitalization. Blood samples were collected at 6.00 a.m., 10.00 a.m., 2.00 p.m., and 7.00 p.m. on the 4^{th} and 8^{th} days of hospitalization. Aggregation in response to arachidonic acid was assessed by impedance aggregometry.

Results. Lower mean platelet aggregation on pantoprazole was observed on the 8^{th} day of hospitalization ($p = 0.03$). A cross-time analysis of platelet aggregation demonstrated statistical significance at two hours and six hours after co-administration of pantoprazole and antiplatelet agents, with the highest absolute difference observed two hours after drugs ingestion. No significant differences in aggregation between study groups were observed on the 4^{th} day of hospitalization. No influence of CYP2C19 polymorphism on the antiplatelet effect of aspirin was observed.

Conclusions. Co-administration of pantoprazole enhances the antiplatelet effect of enteric-coated aspirin in patients with ACS.

Key words: platelet aggregation, acetylsalicylic acid, pantoprazole, proton pump inhibitors, antiplatelet therapy, acute coronary syndrome

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Introduction

Platelet activation induced by atherothrombotic plaque rupture plays a crucial role in the pathology of acute vascular incidents [1]. For that reason, antiplatelet therapy remains the mainstay for the prevention and treatment of heart attack, stroke or acute limb ischaemia [1–3]. Aspirin (ASA, acetylsalicylic acid) is the oldest and most commonly used antiplatelet drug worldwide. On the basis of available data, the guidelines recommend an indefinite low oral dose of ASA for secondary prevention of cardiovascular incidents [4].

Antiplatelet treatment with aspirin and P2Y12 receptor antagonists (ticlopidine, clopidogrel, prasugrel, ticagrelor) carries a substantial risk of gastrointestinal bleeding. For that reason, many patients requiring chronic dual antiplatelet therapy, especially those with high risk of gastrointestinal complications, additionally receive gastroprotective agents.

Some earlier studies have indicated that proton pump inhibitors (PPI) may attenuate the antiplatelet and antipyretic activity of aspirin [5, 6]. Compatible results were recently obtained by Wurtz et al. in a retrospective case-control study [7]. However, our pilot study found a positive interaction between pantoprazole and enteric-coated ASA [8]. Furthermore, PPI influence may be affected by genetic polymorphism of CYP2C19, as this is a principal enzyme in PPI metabolism.

The aim of the current study was to confirm that pantoprazole enhances the antiplatelet effect of enteric-coated aspirin in patients with acute coronary syndrome treated with percutaneous coronary intervention and dual antiplatelet therapy. Moreover, the influence of CYP2C19 polymorphism on the antiplatelet effect of aspirin was assessed.

Methods

Patients

Ninety three consecutive patients (68 men and 25 postmenopausal women) admitted to the Department of Cardiology and Internal Medicine of the Collegium Medicum in Bydgoszcz with a diagnosis of acute coronary syndrome (ACS) and designated to undergo percutaneous coronary intervention (PCI) were prospectively recruited in a randomized, crossover, open-labeled study.

Study design

Patients were randomised to receive low-dose (75 mg) enteric-coated aspirin alone (49 patients) or in combination with pantoprazole 40 mg q.d. (44 patients) for four days, with a subsequent cross-over to receive the alternative treatment regimen for the next four days. Trial exclusion criteria included:

- age less than 18 years;
- clinical indications for PPI usage;
- clinical indications for a prolonged use of heparin or fondaparinux;
- clinical indications for ASA or clopidogrel maintaining daily dose > 75 mg;
- persistent atrial fibrillation or other indications for oral anticoagulants;
- cardiogenic shock on admission or initiation of treatment with vasopressors before PCI;
- a history of chronic heart failure in functional class III or IV according to the New York Heart Association (NYHA), haemodynamically significant valvular heart disease or idiopathic cardiomyopathy;
- thrombocytopenia (< 100,000/mm^3) or history of congenital or acquired bleeding disorder;
- anaemia, defined as haemoglobin level < 10.0 g/dL
- any symptomatic concomitant infection.

All participants provided an informed written consent before the study entry. The study protocol was approved by the Local Ethics Committee.

Concomitant pharmacotherapy

At the first contact with healthcare providers, immediately after establishing the diagnosis of ACS and qualification for PCI, all patients were pre-treated with an intravenous bolus of unfractionated heparin (70 IU/kg, up to 5,000 IU) and oral loading doses of clopidogrel (600 mg) and aspirin (300 mg). At the catheterisation laboratory, a second dose of unfractionated heparin was administered intra-arterially in a weight-adjusted manner (up to 100 IU/kg) or under activated clotting time guidance (to the target range of 200–250 seconds), if abciximab, a blocker of platelet glycoprotein IIb/IIIa, was intended. Abciximab was given at the discretion of the invasive cardiologist. Throughout the hospitalization, clopidogrel was continued in single daily doses of 75 mg given at 8.00 a.m. Post-discharge antiplatelet therapy was planned in accordance with the current European recommendations. Concomitant medications in all patients, including ramipril and bisoprolol, were administered at 8.00 a.m. in doses adjusted for resting heart rate and blood pressure, while atorvastatin was ingested at 8.00 p.m.

Measurement of platelet aggregation

Blood samples were collected into hirudin-containing tubes at 6.00 a.m., 10.00 a.m., 2.00 p.m., and 7.00 p.m. on the 4th and 8th days of hospitalisation. The 4th day of hospitalization was chosen for blood sampling because at this time patients with acute coronary syndrome are usually mobile and leave the coronary care unit, and both aspirin and clopidogrel fully exert their antiplatelet properties. The 8th day (i.e. the fourth day after introducing pantoprazole therapy) was chosen because the four-day period has been assumed to be long enough to allow for interaction between pantoprazole and antiplatelet agents, if one existed. For patients admitted after 7.00 p.m., the next day was regarded as the first day of their hospital stay. Aggregation in whole blood was assessed within two hours of venipuncture on a Multiplate® device (Dynabyte, Munich, Germany), as recommended by the manufacturer [9].

PCI procedure and methodology of platelet aggregation measurements were described previously [8].

CYP2C19 genotyping

Genomic DNA was extracted from whole blood samples according to standard procedures. CYP2C19*17 (CYP2C19_-806_C>T, rs12248560) was genotyped with a commercially available assay (TaqMan Drug Metabolism Genotyping Assay C_469857_10, Applied Biosystems, Foster City, CA, USA) on an ABI Prism Sequence Detector 7000 (Applied Biosystems) according to the manufacturer's instructions. CYP2C19*2 (CYP2C19_681_G>A; rs4244285) was genotyped with a real-time allelic discrimination assay on the same detector. Randomly selected samples were evaluated by direct sequencing of PCR (polymerase chain reaction) products using a BigDye Terminator v. 3.1 sequencing kit and a 3130xl Genetic Analyser (Applied Biosystems). Real-time discrimination and sequencing method gave consistent results. Carriers of loss of function CYP2C19*2 allele were classified as 'poor metabolisers', whereas patients with gain of function CYPC19*17 allele were classified as 'ultra metabolisers'. CYP2C19*1 homozygotes were categorised as normal and CYP2C19*2/*17 heterozygotes as mixed metabolisers.

Statistical analysis

Use of the Shapiro-Wilk test demonstrated that the investigated variables were not normally distributed. Therefore, continuous results were reported as median values and interquartile ranges. The Mann-Whitney U and Kruskal–Wallis tests were used to compare continuous variables between both study groups. For categorical variables, the χ^2 test (with Yates correction if necessary) was used. A value of $p < 0.05$ was considered statistically significant. All computations were carried out with Statistica, version 10.0 (StatSoft, Tulsa, OK, USA).

Results

Statistical analysis showed no significant differences in basic clinical, angiographic or procedural characteristics between both groups.

The comparison of arachidonic acid-dependent platelet aggregation measured on the 8th day of hospitalization revealed statistically significant lower mean platelet aggregation in patients treated with pantoprazole ($p = 0.03$). This tendency was also preserved when aggregation of platelets was analysed separately at different time points. Statistical significance was reached

Table 1. Comparison of arachidonic acid-dependent platelet aggregation [median (lower quartile–upper quartile)]

	6.00 a.m.		10.00 a.m.		2.00 p.m.		7.00 p.m.		mean	
	Pantoprazole (–)	Pantoprazole (+)	Pantoprazole (–)	Pantoprazole (+)	Pantoprazole (–)	Pantoprazole (+)	Pantoprazole (–)	Pantoprazole (+)	Pantoprazole (–)	Pantoprazole (+)
Day 4	16 (9–31)	16 (12–24)	17 (6–25)	16 (10–26)	9 (4–16)	10.5 (4–18)	8 (4–14)	7 (3–15)	12 (8–23)	15 (9–20)
		p = 0.94	p = 0.73		p = 0.80		p = 0.60		p = 0.75	
Day 8	19 (10–32)	16 (7–23)	20 (12–24)	11 (4–22)	13.5 (8.5–19)	9.5 (2–15)	12 (5–16)	10 (4–14)	16 (12–25)	12.5 (7–17.5)
		p = 0.10	p = 0.02		p = 0.04		p = 0.38		p = 0.03	

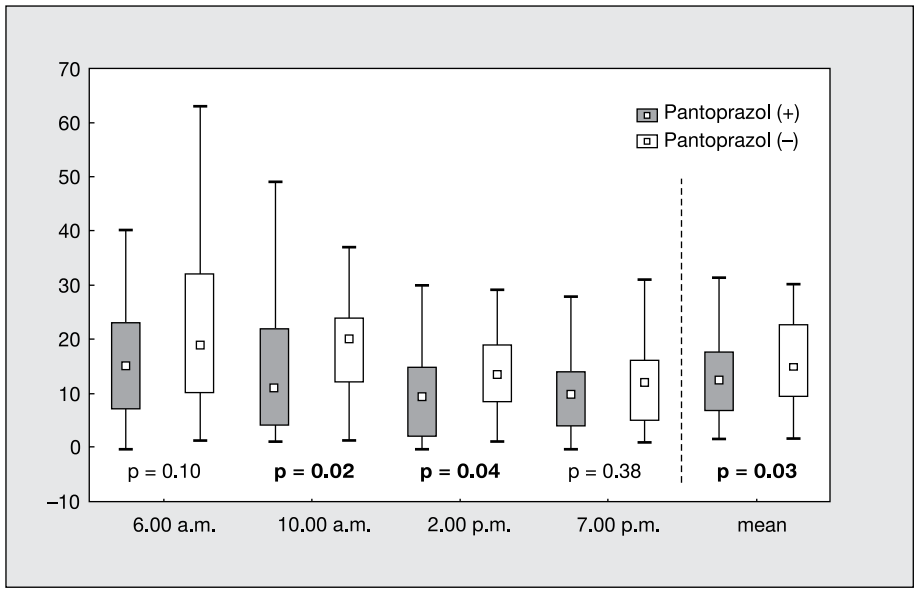

Figure 1. Comparison of arachidonic acid-dependent platelet aggregation on 8th day of hospitalization in patients on dual antiplatelet therapy treated with and without pantoprazole

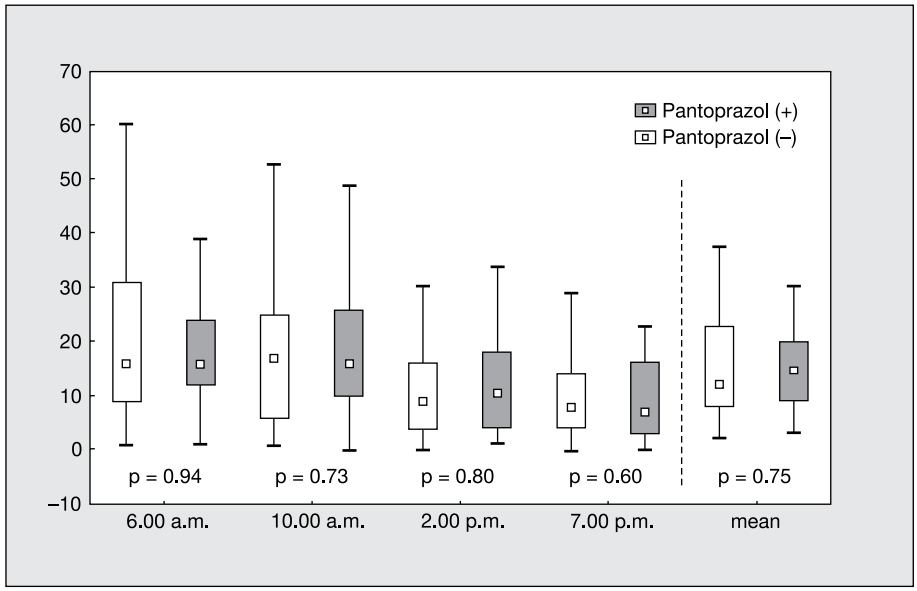

Figure 2. Comparison of arachidonic acid-dependent platelet aggregation on 4th day of hospitalization in patients on dual antiplatelet therapy treated with and without pantoprazole

for measurements obtained at 10.00 a.m. (two hours after morning ingestion of medications) ($p = 0.02$) and 2.00 p.m. (six hours after morning ingestion of medications) ($p = 0.04$). The highest absolute difference in arachidonic acid-dependent aggregation between patients treated with and without pantoprazole was observed at 10.00 a.m. (20 U vs. 11 U) (Tab. 1, Fig. 1).

In contrast, the comparison of platelet aggregation measured on the 4th day of hospitalization showed no significant differences between the study groups (Tab. 1, Fig. 2).

Genetic analysis revealed no relationship between CYP2C19 gene polymorphism and the difference in arachidonic acid-dependent aggregation, either with or without pantoprazole (Tab. 2).

Discussion

Co-administration of PPI is an effective way to prevent gastrointestinal complications in patients receiving

Table 2. Comparison of mean arachidonic acid-dependent platelet aggregation without and with concomitant treatment with pantoprazole according to CYP2C19 gene polymorphism [median (lower quartile–upper quartile)]

Gene polymorphism	Platelet aggregation without pantoprazole	Platelet aggregation with pantoprazole	p†
CYP2C19*1/*1 normal metaboliser n = 29	14 (11–22)	15.5 (9 –19)	0.60
CYP2C19*1/*2 or CYP2C19*2/*2 poor metabolizer n = 27	13 (8–22)	12 (5.5–17.5)	
CYP2C19*1/*17 or CYP2C19*17/*17 ultra metabolizer n = 27	16 (7.5–28)	15 (7–20.5)	
CYP2C19*2/*17 mixed metaboliser n = 6	14 (5–23)	12 (9–13)	

† — p value for heterogeneity in difference between arachidonic acid-dependent aggregation with and without pantoprazole among different genotypes

antiplatelet therapy for the prevention of cardiovascular events [10, 11]. Enteric coating also seems to reduce adverse effects of ASA [12, 13], even though its protective effect remains uncertain [14]. On the other hand, drug interactions may have a significant impact on the effectiveness of therapy, especially in chronic conditions. Two large-scale studies have caused lively discussion and given rise to many experiments on the potential reduction of clopidogrel's effectiveness by proton pump inhibitors [15, 16]. Although ASA usage is very common, the evidence regarding its interaction with gastroprotective agents remains insufficient.

Our results confirmed the findings of our recently published pilot study which, to the best of our knowledge, was the first study showing enhanced effectiveness of ASA with the co-administration of antisecretory agents [9].

Previously conducted experimental studies and retrospective analyses have reported diminished effectiveness of ASA in co-administration with antisecretory agents when a non-enteric-coated formulation of ASA was used [6–8]. Based on the results of our aforementioned study, the first to investigate the impact of PPI on the antiplatelet potency of enteric-coated aspirin, we proposed the influence of enteric coating as an explanation for the discrepancy between our results and other trials [9].

Another, similarly designed, cross-over study was published in 2009 by Adamopoulos et al. [17]. It examined the impact of lansoprazole on platelet aggregation in 24 patients with arterial hypertension treated with a low daily dose (100 mg) of enteric-coated ASA for primary cardiovascular prevention. No significant differences in optical aggregometry, PFA-100 analyser measurements or salicylic acid plasma concentrations were found between the analysed groups. This data suggests that lansoprazole co-therapy does not affect the antiplatelet potency of the enteric-coated form of aspirin. However, it should be stressed that this study was conducted on a relatively small population of patients.

Our present research gave two distinct sets of results. While comparisons of platelets aggregation in the second set of measurements (the 8th day of hospitalization) fully confirmed the findings from our pilot study, results from the first set of measurements (the 4th day of hospitalization) showed no significant interactions between pantoprazole and enteric-coated ASA.

In our pilot study, to explain the observed drug interaction, we suggested higher gastric pH due to concomitant pantoprazole treatment as the reason for enhanced bioavailability of enteric-coated ASA [8]. Plain aspirin is a weakly acidic drug which crosses the mucosa of the gastroduodenal epithelium in its lipophilic state. To a lesser extent, it is transported through the upper part of the intestine where it can be absorbed, in its ionised form, despite the alkaline environment [18]. Acid suppression diminishes the gastric absorption of aspirin because ASA is not absorbed in the stomach when its pH is above 6.5 [19]. For that reason, concomitant usage of PPIs or H2 receptor antagonists interferes with the therapeutic action of plain aspirin. Enteric-coated preparations are created to bypass the stomach and prescribed in an attempt to reduce gastrointestinal side effects. They deliver ASA into the neutral pH environment of the small intestine where absorption of aspirin is possible but considerably delayed, and where bioavailability is reduced [18, 20, 21]. Methacrylic acid, used to form the outer sheet of enteric-coated ASA, remains stable in acid solutions. Active substances are released when pH exceeds 5.5. In normal conditions, these drugs pass intact through the upper part of the gastrointestinal tract and do not release active substances unless they reach the duodenum or more distal parts of the intestine. The addition of PPI, by alkalising gastric pH, causes destabilisation of the methacrylic acid sheath in the stomach and, in consequence, rapid absorption with higher bioavailability.

This postulated mechanism seems to be supported by the fact that, in both our studies, the highest

difference in medians of arachidonic acid-dependent platelet aggregation was found two hours after morning ingestion of the investigated drugs.

Interestingly, our present study found no differences in platelet aggregation comparing results in the first set of measurements done on the 4th day after myocardial infarction onset and PCI. Coronary angioplasty causes atherothrombotic plaque rupture, endothelial injury and arterial wall damage. These, in turn, enhance coagulation and the release of inflammatory and chemoattractant factors, which in consequence may activate platelets [22–25]. These phenomena provide an explanation of the results obtained by Siller-Matula et al. in a study assessing platelet function at different time points after PCI [26]. In this study, the antiplatelet effect of clopidogrel and aspirin was diminished immediately post PCI. In the aforementioned studies, the proinflammatory and hypercoagulability state seemed to normalise within 24 hours. However, its influence on platelet function may, to some extent, persist for the whole platelet lifespan, which in normal conditions is up to ten days.

It is important to stress that all patients in our study were pretreated with a loading dose of uncoated ASA once the diagnosis of ACS was established. Since ASA-induced platelet cyclooxygenase-1 (COX-1) inactivation is irreversible, its restoration depends on new platelets being produced in the bone marrow. That is why, in physiological conditions, full COX-1 restoration may take up to ten days [27].

This means that both series of measurements performed in our study, particularly the first one from the 4th day of hospitalization, might have been influenced by thrombogenic and proinflammatory factors released during ACS and PCI, or by the antiplatelet effect of the loading dose of ASA. These factors may have a stronger impact on platelet aggregation than the interaction with pantoprazole and this could be the reason for the lack of interaction observed in the first series of measurements.

All PPIs are extensively metabolised in the liver by cytochrome P450 enzymes CYP2C19 and CYP3A4. The main pathway of pantoprazole inactivation is demethylation, by CYP2C19 [28]. Gene polymorphism of that enzyme, by influencing the plasma concentration of pantoprazole, might also have an impact on interaction with enteric-coated ASA. However, our present study did not confirm a relationship between CYP2C19 gene polymorphism and the difference in arachidonic acid-dependent aggregation with or without pantoprazole.

The main limitation of our study is that we have not ultimately proven that the observed differences in platelet aggregation are due to changes in drug absorption in the digestive tract. Such confirmation may come from direct measurements of blood ASA concentrations. This would however be very difficult to perform as the plasma half-life of ASA is relatively short (about 15 minutes) because of rapid hydrolysation to salicylic acid in erythrocytes and the liver [23]. An indirect approach to support our theory might be the measurement of platelet aggregation one hour after drugs ingestion.

Another limitation was the relatively short (four days) period with and without concomitant pantoprazole treatment in our cross-over designed study. This enabled study completion during one hospital stay, assuring 100% adherence to the therapy. On the other hand, it was probably the reason why no interaction between enteric-coated ASA and pantoprazole was seen in the first series of measurements. In this setting, an impact of the acute phase of ACS and ASA loading dose cannot be excluded. There was also no washout period after pantoprazole treatment in patients who received the drug in the first phase of the study. Therefore, performing a similar study but providing measurements later, after the onset of ACS together with proper washout periods, is worth consideration.

In conclusion, our study indicates that co-administration of pantoprazole enhances the antiplatelet effect of enteric-coated aspirin in ACS patients

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