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Pantoprazole may enhance antiplatelet effect of enteric-coated aspirin in patients with acute coronary syndrome

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Abstract

Background: *Antiplatelet therapy has proven beneficial in the treatment of cardiovascular disease. Proton pump inhibitors (PPIs) are commonly used for gastroprotection in patients receiving antiplatelet therapy. Several trials have been carried out to establish interactions between PPIs, clopidogrel and soluble formulations of aspirin, but no studies with PPIs and enteric-coated (EC) forms of aspirin have been conducted. The aim of this study was to assess if concomitant pantoprazole usage influences antiplatelet effect of EC aspirin in patients with acute coronary syndrome treated with percutaneous coronary intervention (PCI) and dual antiplatelet therapy.*

Methods: *Thirty-one consecutive patients were prospectively enrolled in the randomized, crossover, open-labelled designed study. The first 16 patients were given orally 40 mg of pantoprazole for the first four days while the next 15 subjects were treated with pantoprazole from the fifth to the eighth day of hospitalisation. Blood samples were collected at 6.00 a.m., 10.00 a.m., 2.00 p.m., and 7.00 p.m. on the fourth and eighth day of hospitalization. Aggregation in response to arachidonic acid was assessed in the whole blood on a new generation impedance aggregometer.*

Results: *Lower overall platelet aggregation in patients treated with pantoprazole ($p < 0.03$) was observed. When aggregation of platelets was analyzed separately at different times, the differences reached statistical significance six hours after the administration of pantoprazole and antiplatelet agents. The highest absolute difference in arachidonic acid-dependent aggregation was observed two hours after drug ingestion.*

Conclusions: *Co-administration of pantoprazole may enhance the antiplatelet effect of enteric-coated aspirin in patients with acute coronary syndrome undergoing PCI.* (Cardiol J 2009; 16, 6: 535–544)

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

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Introduction

Acute coronary syndrome (ACS), the leading cause of death in most European countries, occurs as a result of thrombus formation within the coronary artery lumen [1]. Coronary plaque rupture in ACS, or that associated with percutaneous coronary intervention (PCI), releases thrombogenic substances into the circulation, stimulating platelet activation and aggregation [2]. As dual antiplatelet therapy has proven beneficial in the treatment of cardiovascular disease and decreasing the occurrence of stent thrombosis, current guidelines recommend a combination of aspirin and clopidogrel for patients with ACS and/or undergoing PCI [3, 4].

Aspirin has been widely used in the primary and secondary prevention of cardiovascular events since many trials demonstrated its beneficial effect [5–7]. Despite this strong evidence of aspirin's protective effect, there is a group of patients who suffer from acute coronary syndrome due to persistent platelet hyperactivity. This 'aspirin resistance' has been reported in 5% to 40% of patients, depending on the assessment method [8–10]. A number of clinical studies and a recent meta-analysis conducted by Krasopoulous et al. have correlated aspirin resistance with unfavorable long-term clinical outcomes, not only in patients with coronary artery disease (CAD) but also in patients with ischemic stroke or peripheral arterial disease [11–14].

Beside its enormous cardioprotective effect, antiplatelet treatment carries substantial side effects: mainly gastrointestinal ulceration and bleeding [15]. Observational studies [16, 17], as well as Antithrombotic Trialists' Collaboration meta-analysis [18], have reported a two to four-fold increased risk of upper gastrointestinal events when a low-dose of acetylsalicylic acid (ASA) is administered.

For that reason, patients receiving a dual antiplatelet therapy after coronary stenting are commonly treated with proton pump inhibitors for gastrointestinal protection. Recent guidelines published by the American Heart Association, the American College of Gastroenterology and the American College of Cardiology recommend proton pump inhibitors (PPI) therapy for the majority of patients treated with antiplatelet agents, including all patients aged 60 years or older and patients receiving dual antiplatelet therapy [15]. However, it was demonstrated that PPIs may attenuate the antiplatelet and antipyretic effect of aspirin [19, 20] in the rat model.

Buffered or enteric-coated preparations of ASA are proposed as another approach to gastroprotection of patients requiring antiplatelet treatment. As far as we know, no trial assessing the pharmacological or clinical interaction between enteric-coated forms of aspirin and proton pump inhibitors has been conducted, while data regarding interaction between plain aspirin and PPIs is sparse.

The aim of our study was to assess whether concomitant pantoprazole usage influences the antiplatelet effect of enteric-coated aspirin in patients with acute coronary syndrome treated with percutaneous coronary intervention and dual antiplatelet therapy.

Methods

Patients

Thirty-one consecutive patients (22 men and nine post-menopausal women) admitted to the Department of Cardiology and Internal Medicine of the Collegium Medicum in Bydgoszcz with a diagnosis of ACS, and designated to undergo PCI, were prospectively recruited into the randomized, crossover, open-labelled study (Fig. 1).

Study design

Patients were randomized to receive low-dose (75 mg) enteric-coated aspirin alone (16 patients) or low-dose enteric-coated aspirin plus 40 mg pantoprazole (15 patients) for four days. Then participants were 'crossed over' to receive the alternative treatment regime for the next four days. Trial exclusion criteria were:

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

All participants provided informed written consent before entering the study. The clinical chara-

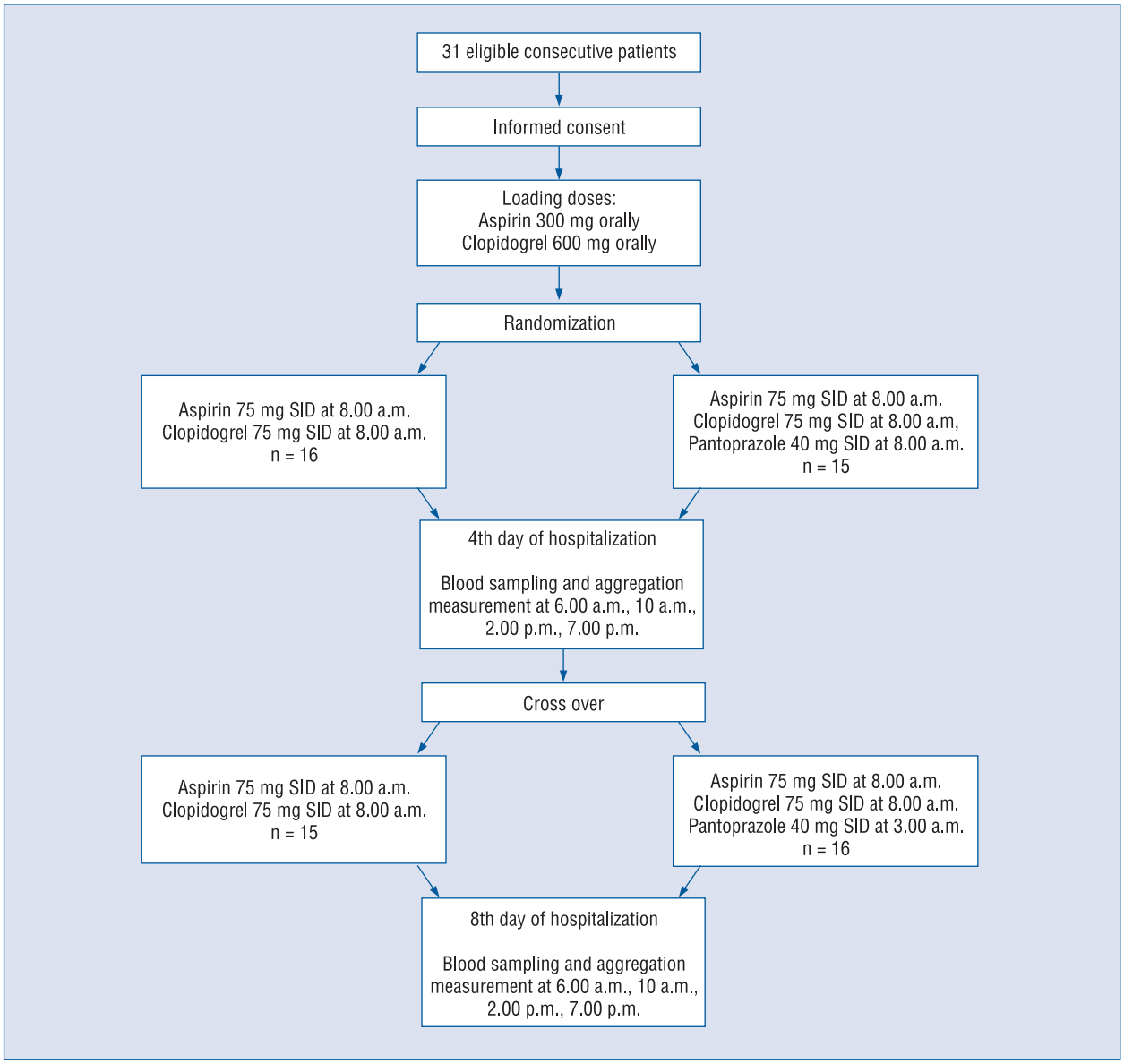

Figure 1. Study design.

cteristics of the patient population are presented in Table 1. The study protocol was approved by the Local Ethics Committee.

Concomitant pharmacotherapy

At the first contact with health care providers immediately after the diagnosis of ACS and decision of PCI, all patients were pretreated with an intravenous bolus of unfractionated heparin (70 IU/kg, but not more than 5000 IU) and oral loading doses of clopidogrel (600 mg) and aspirin (300 mg). At the catheterization laboratory, a second dose of unfractionated heparin was intra-arterially administered in a weight-adjusted manner (up to 100 IU/kg) or under activated clotting time guidance (to the target range 200–250 s), 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 doses of 75 mg given at 8.00 a.m. Post-discharge antiplatelet therapy was planned in accordance with current European recommendations. Concomitant medications in all patients, included ramipril and bisoprolol, were pro-

Table 1. Clinical characteristics of the study population.

	Whole population (n = 31)	Patients initially treated with pantoprazole (n = 15)	Patients initially treated without pantoprazole (n = 16)
Age (years)	60.0 (53.0–68.0)	60.0 (57.0–65.0)	60.5 (53.0–69.0)
Gender [male/female]	22/9	10/5	12/4
Final clinical diagnosis:			
UA	1	1	0
NSTEMI	2	0	2
STEMI	28	14	14
Time from symptom onset [h]	3.5 (2.0–7.0)	4.2 (2.0–7.0)	3.1 (1.5–6.3)
CK-max [U/L]	215.0 (73.0–1178.0)	192.0 (68.0–1050.0)	230.0 (75.0–1255.0)
CK-MBmax [U/L]	34.0 (16.0–182.0)	31.0 (14.0–175.0)	38.0 (18.0–210.0)
TnImax [ng/mL]	1.993 (0.690–31.200)	1.788 (0.548–28.700)	2.243 (0.815–36.500)
LVEF (%)	48.0 (40.0–50.0)	46.0 (40.0–50.0)	49.0 (42.0–51.0)
Risk factors of coronary artery disease:			
Body mass index [kg/m^2]	27.2 (25.6–29.8)	27.3 (26.9–29.4)	26.8 (25.0–30.7)
Arterial hypertension	22	10	12
Diabetes mellitus	13 including 10 newly diagnosed patients	7 including 5 newly diagnosed patients	6 including 5 newly diagnosed patients
Current smokers	15	8	7
History of smoking	4	2	2
Positive family history	4	2	2
Total cholesterol [mg/dL]	216.0 (192.0–244.0)	216.0 (200.0–234.0)	216.5 (189.0–244.0)
LDL cholesterol [mg/dL]	148.0 (125.0–175.0)	148.0 (122.0–161.0)	148.0 (129.0–175.0)
HDL cholesterol [mg/dL]	39.0 (34.0–41.0)	39.0 (36.0–42.0)	39.0 (31.0–41.0)
Triglycerides [mg/dL]	132.0 (86.0–112.0)	140.0 (86.0–211.0)	120.0 (74.0–193.0)

No statistically significant differences between both arms of the study group were observed; UA — unstable angina; STEMI — ST elevation myocardial infarction; NSTEMI — non-ST elevation myocardial infarction

vided at 8.00 a.m. in doses adjusted for resting heart rate and blood pressure, and atorvastatin was administered at 8.00 p.m.

Percutaneous coronary interventions

Coronary angiography and PCI procedures were performed using the standard technique via the femoral artery with the aid of an Integris Allura device (Philips, the Netherlands). Non-ionic low-osmolar contrast media were applied. During angiography, at least five left coronary artery and three right coronary artery projections were taken after previous administration of 0.3 mg nitroglycerine into the coronary vessels, if arterial pressure was sufficient. Epicardial coronary flow was assessed according to the Thrombolysis In Myocardial Infarction (TIMI) scale. Bare metal stents were implanted in all patients. The optimal direct effect of the intervention was assigned when no residual stenosis, or a stenosis of less than 20% of the reference segment diameter, was observed. Detailed characteristics of the procedures are displayed in Table 2.

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 fourth and eighth days of hospitalization. The fourth day of hospitalization was chosen because at this time the patient with acute coronary syndrome is usually mobile, has usually left the coronary care unit, and both aspirin and clopidogrel fully exert their antiplatelet properties. The eighth day (fourth day after introducing pantoprazole therapy) was chosen because it was assumed that four days are enough to stabilize interaction of pantoprazole and antiplatelet agents, if any such interactions exist. If a patient was admitted after 7.00 p.m., the following day was counted as the first day of hospital stay.

Table 2. Angiographic and procedural characteristics of the study population (n = 31).

	Whole population (n = 31)	Patients initially treated with pantoprazole (n = 15)	Patients initially treated without pantoprazole (n = 16)
Coronary artery disease:			
Single-vessel	11	6	5
Multivessel	20	9	11
Localization of culprit lesion:			
Left anterior descending artery	12	6	6
Diagonal branch	1	0	1
Intermediate artery	1	0	1
Circumflex artery	4	2	2
Obtuse marginal artery	2	2	0
Right coronary artery	11	5	6
Baseline blood flow in the culprit vessel:			
TIMI 0	16	9	7
TIMI 1	3	1	2
TIMI 2	2	0	2
TIMI 3	10	5	5
Final blood flow in the culprit vessel:			
TIMI 2	2	1	1
TIMI 3	29	14	15
Usage of abciximab	8	3	5
Direct stenting	9	5	4
Multivessel primary PCI	9	3	6
Number of implanted stents:			
0	2	1	1
1	16	7	9
2	6	3	3
3	6	4	2
4	1	0	1
Total length of implanted stents [mm]	18.0 (13.0–25.0)	19.0 (15.0–25.0)	15.0 (12.0–28.0)
Maximal stent or balloon diameter [mm]	3.0 (2.5–4.0)	3.0 (2.5–3.0)	3.2 (2.5–4.0)
Maximal inflation pressure [atm]	18.0 (16.0–22.0)	20.0 (18.0–22.0)	17.0 (14.0–18.0)
Outcome of primary PCI			
Effective	31	15	16
Ineffective	0	0	0
Revascularization:			
Complete	23	10	13
Incomplete	8	5	3
Qualification for further treatment:			
Conservative	26	12	14
PCI	5	3	2

No statistically significant differences between both arms of the study group were observed; PCI — percutaneous coronary intervention

Aggregation in the whole blood was assessed within two hours of the venipuncture on a new generation impedance analyzer with multiple electrode aggregometry according to the manufacturer's instructions [21]. This method can detect the effect of antiplatelet treatment and its results correlate well with light transmission aggregometry [22]. The whole procedure of platelet aggregation measurement with a Multiplate® device (Dynabyte, Munich, Germany) was performed in approximately ten

minutes. Whole blood, which was utilized in our study, is the physiological environment where platelet function takes place *in vivo*. Moreover, the use of whole blood for *in vitro* testing eliminates the need for the time-consuming centrifugation steps required to obtain the platelet-rich plasma necessary for light transmission aggregometry. Therefore, it must be stressed that impedance aggregometry and light transmission aggregometry measure different aspects of platelet function.

Impedance aggregometry results reflect interactions between platelets and red and white cells, while light transmission aggregometry does not [23].

The principle of impedance aggregometry is based on the fact that platelets get sticky upon activation, and therefore have a tendency to adhere and aggregate on metal sensor wires in the test cell. One Multiplate® test cell incorporates two independent sensor units, each consisting of two silver-coated, highly conductive wires. When activated platelets adhere to the sensor wires, the electrical resistance between the wires rises, which is continuously registered. The instrument detects the impedance change of each sensor separately and transforms it into arbitrary aggregation units (AU) that are plotted against time. The area under the aggregation curve (AUC) is an estimator of platelet aggregation that was evaluated in our study. It is affected by the total height of the aggregation curve as well as by its slope, and is best suited to express the overall platelet activity. Aggregation, quantified as the area under the curve, is displayed in arbitrary units (10 AU × min = 1 U). In previous studies AUC highlighted as the parameter with the highest diagnostic power [21, 24]. To assess a platelet response to aspirin we applied ASPI test (Dynabyte, Munich, Germany) which uses arachidonic acid that serves as the substrate of the cyclooxygenase for synthesis of a potent platelet agonist, thromboxane A2. Using this fast and standardized method, comprehensive information on platelet function and antiplatelet therapy can be obtained. Reported intra-assay coefficient of variations (CV) for ASPI test was 11.5%, while intra-individual CV was 11.4% [23]. The manufacturer recommends 30 U as the cut-off value associated with platelet hyperaggregability in patients on aspirin therapy.

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. Comparisons between groups were analyzed with the Mann-Whitney unpaired rank sum test, whereas the Wilcoxon matched-paired rank sum test was used for comparisons within groups. A value of $p < 0.05$ was considered statistically significant. All computations were carried out with Statistica, version 8.0 (StatSoft, Tulsa, USA).

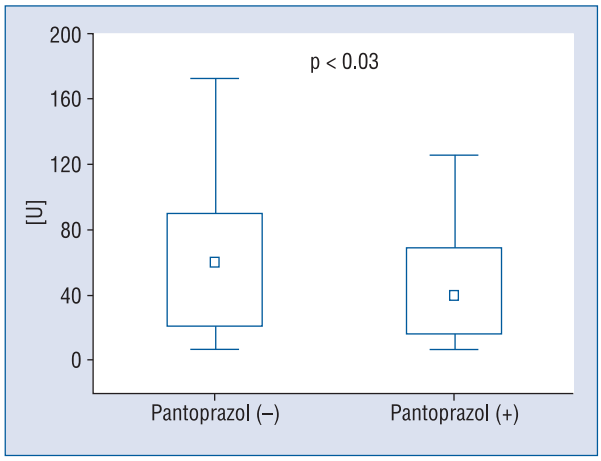

Figure 2. Comparison of overall (obtained from four daily measurements) circadian arachidonic acid-dependent platelet aggregation in patients on dual antiplatelet therapy treated with and without pantoprazole.

Results

The two arms of the study group did not differ in terms of clinical characteristics and angiographic features (Table 1, 2).

The comparison of overall circadian arachidonic acid-dependent platelet aggregation in patients with ACS on dual antiplatelet therapy revealed substantial, statistically significant, lower platelet aggregation in patients treated with pantoprazole ($p < 0.03$) (Fig. 2). The tendency towards lower aggregation ability in a group treated with pantoprazole was preserved when the aggregation of platelets was analyzed separately at different times (Fig. 3). These differences, however, reached the point of statistical significance only at 2.00 p.m. (4 U *vs*. 10 U; $p < 0.04$). The highest absolute difference in arachidonic acid-dependent aggregation between patients treated with pantoprazole and the control group was observed at 10.00 a.m: two hours after administration of PPI along with both antiplatelet agents (10 U *vs*. 19 U; $p = 0.10$).

Detailed comparisons of arachidonic acid-dependent platelet aggregation between both arms of the study group revealed lower values of platelet reactivity on Day 8 in pantoprazole treated patients; that reached statistical significance at 10.00 a.m. (Table 3).

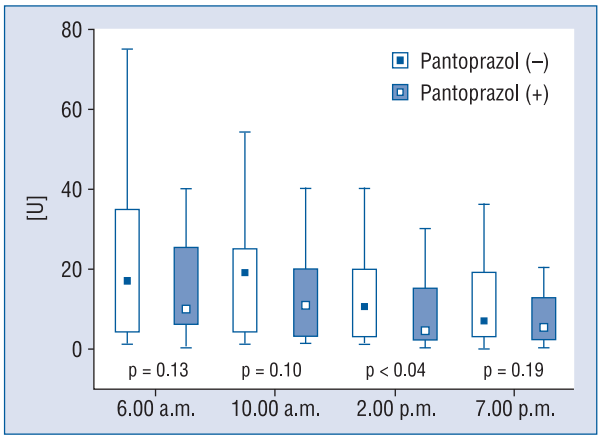

Figure 3. Comparison of arachidonic acid-dependent platelet aggregation at different times in patients on dual antiplatelet therapy treated with and without pantoprazole.

15.5% of ASPI results of patients treated with pantoprazole and 17.7% of results in the control group were above the cut-off values that, according to the producer, may be associated with aspirin resistance.

Discussion

The present study provided us with unexpected results. Previous animal trials had reported diminished effectiveness of ASA in co-administration with antisecretory agents when a non-enteric-coated formulation of aspirin was used [19, 20, 25]. To the best of our knowledge, this is the first up-to-date study investigating the influence of PPI on antiplatelet effect of enteric-coated formulations of aspirin. We conclude that enteric-coating, altering the pharmacokinetics of drugs, may be a reason for the discrepancy between our study and earlier conducted trials.

Plain aspirin is a weakly acidic drug (pKa = = 3.5). It 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 despite alkaline environment in its ionized form [26]. Soluble forms of aspirin achieve peak blood concentrations 30 to 40 minutes after ingestion [26]. Its bioavailability is approximately 50% [27]. Aspirin is partly hydrolyzed by abundant mucosal esterases to salicylic acid (SA), and it is inactive in antiplatelet matter metabolite [20, 28]. Hydrolyzation of ASA to SA in gastrointestinal tract occurs mainly in the intestine, and to a lesser extent in the stomach, where in nor-

Table 3. Comparison of arachidonic acid-dependent platelet aggregation for Day 4 and Day 8 for each tested time point for both arms of the study group.

	6.00 a.m.		10.00 a.m.		2.00 p.m.		7.00 p.m.	
	Pantoprazole (–)	Pantoprazole (+)	Pantoprazole (–)	Pantoprazole (+)	Pantoprazole (–)	Pantoprazole (+)	Pantoprazole (–)	Pantoprazole(+)
Day 4	16.0 (4.0–35.0)	18.0 (8.0–19.0)	13.5 (3.0–22.0)	18.0 (10.0–20.0)	8.0 (3.0–21.0)	6.0 (2.0–15.0)	5.5 (3.0–18.0)	3.0 (2.0–9.0)
	NS		NS		NS		NS	
Day 8	21.0 (6.0–28.0)	9.0 (2.0–25.0)	24.0 (6.0–37.0)	4.0 (2.0–16.0)	15.0 (2.0–20.0)	4.0 (1.0–13.0)	11.0 (2.0–23.0)	5.0 (2.0–20.0)
	NS		p < 0.03		NS		NS	

mal conditions esterases are less active due to lower pH. Giraud et al. [20] reported that elevated gastric pH was related to substantially lower ASA concentration in the peripheral blood sample when concentrations of SA remains unchanged.

Enteric-coated preparations are created to bypass the stomach and prescribed in an attempt to reduce gastrointestinal side effects [29]. They deliver ASA into the neutral pH environment of the small intestine. In such an environment, the absorption of aspirin is delayed, with peak plasma concentrations achieved three to four hours after oral administration, with reduced bioavailability [26, 30, 31]. Most studies indicate that some subjects treated with low-dose enteric-coated (EC) aspirin fail to achieve minimum thresholds of effective platelet inhibition. Maree et al. [30] found that EC ASA is less effective than plain aspirin in patients with stable cardiovascular disease in terms of laboratory measurements. Similarly, Alberts et al. [32], in a study of patients with cerebrovascular disease, observed normal platelet function despite ASA treatment in a substantially higher percentage of patients when enteric-coated formulations were used. Cox et al. [31] assumed that 75 mg of enteric-coated aspirin delivers a dose of equivalent to 50 mg of plain aspirin in healthy subjects which may predispose to incomplete inhibition of COX in some (especially heavier) individuals.

The concomitant use of PPIs for gastrointestinal protection may also interfere with the therapeutic action of aspirin. Acid suppression with PPI diminishes the gastric aspirin absorption because ASA is not absorbed into the stomach when its pH is greater than 6.5. At pH 3.5–6.5 gastric absorption is lower than in the small intestine where ASA can be absorbed to an appreciable extent in its ionized form [33]. Rising gastric pH can also increase the potential for mucosal esterases to hydrolyze ASA to its inactive SA form [25]. Similarly, as with enteric-coating formulations, this mechanism may be crucial when aspirin is used at low doses in the prophylaxis of stroke or coronary heart disease [20]. Lichtenberg et al. [19] showed that not only PPIs but also ranitidine or cimetidine to a similar extent attenuate antipyretic activity of aspirin in rats [20]. It supports the theory that increased gastric pH is the main reason for reduced aspirin bioavailability when PPI is co-administered. A human study conducted on healthy subjects with ranitidine by Lev et al. [34] reached similar conclusions. On the other hand, Inarrea et al. [35] in a study similarly designed to ours but using plain aspirin and healthy volunteers, found no differences in platelet lumiaggregation and skin bleeding time when low dose aspirin was co-administered with omeprazole. It should however be emphasized that in this study only 14 subjects were enrolled and a tendency to lower plasma ASA concentration on therapy with pantoprazole was observed. As shown above, other antacids similarly to PPIs, lower the effect of aspirin. Hence, it is likely that interaction between PPI and aspirin is a pharmacokinetic change, as discussed above, rather than any pharmacodynamic interaction.

In clinical use there are myriad ASA formulations including various enteric-coated preparations. The outer sheet of EC ASA, used in our study, is composed mainly of methacrylic acid (MAA) which is one of the commonly used substances in the production of enteric-coated drug formulations worldwide. Methacrylic acid is stable in acid solutions. Active substances are released from EC formulations when in pH > 5.5. This means that, in normal conditions, these drugs pass intact through the upper gastrointestinal tract and do not release their active substances until they reach the duodenum or a more distal part of the intestines.

In our study we found higher antiplatelet potential of low-dose methacrylic acid EC ASA when it was co-administered with pantoprazole.

The likeliest explanation, in the light of earlier quoted studies, is better bioavailability of methacrylic acid EC preparation in alkalized gastric juice. As pH > 5.5 does not normally exist in the stomach, addition of PPI causes earlier destabilization of the methacrylic acid sheath. If gastric pH stays between 5.5 (needed for the methacrylic acid sheath to dissolve) and 6.5 (the pH limit for gastric ASA absorption) aspirin, at least to some extent, may be assimilated in the stomach. However, gastric pH, obtained due to co-administration of pantoprazole might be higher. In this case, the explanation of our observation might be that, after sheath depolymerization, aspirin reached the duodenum already in its soluble form, thus assuring rapid absorption. This possible mechanism may be supported by the fact that the highest (though not statistically significant) difference in medians of arachidonic acid-dependent platelet aggregation was found at two hours after morning tablets ingestion. This timing is between the period needed for plain aspirin (30–40 min) and EC formulations (3–4 h) to reach top plasma concentrations. Significant difference in medians of arachidonic acid-dependent platelet aggregation at four hours after ingestion suggests that pantoprazole does not only accelerate absorption but also enhances the overall bioavailability.

A potential limitation of our study is the fact that we have not ultimately proven that observed differences in aggregation are due to changed absorption. The confirmation would be direct measurements of blood ASA concentrations at different time points (30, 60, 120, 240 min) after oral administration of soluble *vs*. enteric-coated ASA, in co-administration with PPI. However, as shown in previous studies, plasma half-life of ASA is relatively short (about 15 min) because after absorption it is rapidly hydrolyzed to inactive salicylic acid by esterases in the erythrocytes of the portal circulation and in the liver [36]. For that reason, the main effect of ASA in acetylating platelet COX-1 is restricted to the portal circulation and the antiplatelet effect of aspirin may not correspond to its systemic concentrations [25]. Another approach to support our theory could be measuring platelet aggregation one hour after drugs ingestion.

A second shortcoming is that although we performed a crossover designed study to exclude impact of acute phase of ACS, there was no washout period after usage of pantoprazole in the first 16 enrolled patients. Also, the periods with and without concomitant pantoprazole treatment were relatively short (four days). However, this design meant we could conduct the whole study during the hospital stay, assuring 100% adherence to the therapy.

Our findings seem to agree with recent guidelines which recommend combining ASA and PPIs instead of switching to clopidogrel in high risk gastrointestinal bleeding patients. The same recommendations promote broad PPI gastroprotection for patients receiving dual antiplatelet therapy [15]. In our opinion, however, these guidelines should be applied carefully since this approach may potentially diminish the antiplatelet effect of clopidogrel because interactions between clopidogrel and PPIs are not fully recognized [37–42].

Conclusions

To conclude, co-administration of pantoprazole may enhance the antiplatelet effect of enteric-coated aspirin in patients with ACS undergoing PCI. To recommend pantoprazole use in all patients receiving dual antiplatelet therapy, its potential negative interaction with clopidogrel would have to be ultimately excluded.

Acknowledgements

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