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The antiplatelet effect of aspirin is reduced by proton pump inhibitors in patients with coronary artery disease

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ABSTRACT

Objective To evaluate the effect of proton pump inhibitors (PPIs) on the platelet response to aspirin in patients with coronary artery disease (CAD).

Design Case—control study.

Patients 418 stable patients with CAD, 54 of whom were treated with PPIs. All patients were treated with non-enteric coated aspirin 75 mg/day and received no other antithrombotic drugs.

Main outcome measures Platelet aggregation was measured by Multiplate (Dynabyte, Munich, Germany) whole blood aggregometry induced by arachidonic acid 1.0 mmol/l and expressed as area under the aggregation curve (aggregation units*min). Platelet activation was assessed by soluble serum P-selectin. Compliance was confirmed by serum thromboxane B_2 levels.

Results The distribution of age, sex, body mass index, blood pressure, family history of ischaemic heart disease, smoking, diabetes and the number of previous ischaemic events did not differ between groups. All patients were compliant with aspirin treatment according to serum thromboxane B_2 levels. Platelet aggregation (median 180 (interquartile range 119—312) vs 152 (84—226) aggregation units*min, p=0.003) and soluble serum P-selectin levels (88.5 (65.2—105.8) vs 75.4 (60.0—91.5) ng/ml, p=0.005) were significantly higher in patients treated with PPIs. Furthermore, these patients had significantly higher serum thromboxane B_2 levels (geometric mean 1.29 (95% CI 0.96 to 1.72) vs 0.92 (0.84 to 1.01) ng/ml, p=0.01).

Conclusions Patients with CAD treated with PPIs had a reduced platelet response to aspirin, as shown by increased residual platelet aggregation and platelet activation, compared with patients with CAD not taking PPIs. Concomitant use of aspirin and PPIs might reduce the cardiovascular protection by aspirin.

INTRODUCTION

Aspirin is the mainstay of secondary antithrombotic treatment. Accordingly, low-dose aspirin lowers the risk of vascular events by 32% in high-risk patients.[1] However, platelet response to aspirin is variable and in some patients platelet aggregation is inhibited less than expected.[2] These patients might be at an increased risk of cardiovascular events.[3 4]

Aspirin treatment carries a risk of dyspepsia and upper gastrointestinal bleeding, and thus is often combined with a proton pump inhibitor (PPI). PPIs protect the gastric mucosal barrier by suppressing gastric acid production.[5] Under physiological acidic conditions, aspirin is absorbed in its lipid state by passive diffusion across the gastric mucosal membrane according to the pH partition hypoth-

esis.[6] PPIs exert their antacid effect by inhibiting the H^+/K^+-exchanging ATPase of the gastric parietal cells, thus raising intragastric pH.[7] In fact, the pH potentially rises above the pK_a (3.5) of acetylsalicylic acid, causing a pronounced reduction in the lipophilicity of aspirin.[8] According to previous studies, such chemical changes might compromise the bioavailability and therapeutic efficacy of aspirin.[9—11]

Previous studies have examined the effect of PPIs on the antiplatelet effect of clopidogrel.[12 13] Presumably, PPIs attenuate the antiplatelet effect of clopidogrel by competitively inhibiting the cytochrome P450 (CYP) isoenzyme system, in particular CYP2C19, which is responsible for converting clopidogrel to its active metabolite.[14] Less attention has been paid to the potential drug interaction between PPIs and aspirin, although aspirin remains the most commonly used drug world wide. However, any interaction between PPIs and aspirin remains to be established.

P-selectin is a cell adhesion molecule stored in the α-granules of platelets. If not expressed on the platelet surface, P-selectin might be released into the blood as soluble P-selectin. Soluble serum P-selectin (sP-selectin) is regarded as a marker of platelet activation.[15]

Serum thromboxane B_2 (S-TxB_2) measurements reliably reflect endogenous thromboxane A_2 production, which occurs largely, albeit not exclusively, in platelets.[16] Hence, S-TxB_2 is regarded as the most specific test for measuring the inhibitory effect of aspirin on platelets.[17 18]

The main purpose of this study was to investigate whether patients with coronary artery disease (CAD) treated with PPIs had a reduced platelet response to aspirin, as shown by increased residual platelet aggregation and platelet activation, compared with patients with CAD not taking PPIs.

METHODS

Design and study population

We performed a case—control study including 418 patients angiographically diagnosed with CAD. Among these, 54 patients received PPI treatment.

Patients were identified in the Western Danish Heart Registry and enrolled from November 2007 through April 2009 according to predefined inclusion and exclusion criteria. The Western Danish Heart Registry collects data on patient and procedure characteristics for all interventions performed in interventional centres in the western part of Denmark.[19]

Patients ≥18 years of age with angiographically verified CAD receiving low-dose (75 mg) non-enteric

coated aspirin treatment were included in the study. Exclusion criteria were aspirin intolerance, any acute or chronic disease (apart from CAD), use of anticoagulants or any drugs known to affect platelet function (including clopidogrel and non-steroidal anti-inflammatory drugs), pregnancy, gastrointestinal bleeding within the past month, platelet count $<120 \times 10^9$/l, any ischaemic event or revascularisation procedures (percutaneous coronary intervention or coronary artery bypass grafting) within the previous 12 months and inability to give informed consent.

All patients were treated with aspirin 75 mg/day before and during study participation. Current drugs, including the use of PPIs and aspirin, was registered on the day of blood sampling and subsequently confirmed by reviewing hospital records.

Written informed consent was obtained from all participants. The study was conducted in agreement with the Helsinki-II declaration, and the study was approved by the Central Denmark Region Committees on Biomedical Research Ethics.

Laboratory measurements

Standardised blood sampling was performed 1 h after aspirin intake. Patients rested for 30 min before sampling in the supine position. Samples were drawn from an antecubital vein into vacuum tubes through a 19G butterfly needle using a minimum of stasis.

Platelet aggregation was measured by the Multiplate analyser (Dynabyte, Munich, Germany). Mutiplate is a whole-blood impedance platelet aggregometer providing simultaneous duplicate measurements.[20] All platelet aggregation analyses were performed within 2 h of sampling. Blood was collected in 3.6 ml tubes containing 3.2% sodium citrate and in 3 ml tubes containing hirudin 25 μg/ml. Platelet aggregation was induced by arachidonic acid (1.0 mmol/l). Results are reported as area under the aggregation curve (aggregation units (AU)*min).[20] A quality control of a sample from a person with normal coagulation status was performed each day in order to ensure that agonist solutions were appropriately prepared.

sP-selectin was determined by ELISA according to the manufacturer's instructions (R&D Systems, Minnesota, USA). Blood was collected in non-anticoagulated glass tubes and allowed to clot at room temperature for 30 min before centrifugation for 15 min at 1000 g. The supernatant serum was recovered and stored at −80°C.

S-TxB$_2$ levels were determined according to Patrono et al[21] with the modifications that serum was collected after 1 h of clotting and that S-TxB$_2$ was measured by ELISA (Cayman Chemical, Michigan, USA). Blood was collected in non-anticoagulated glass tubes and allowed to clot at 37°C for 1 h. Subsequently, it was centrifuged for 10 min at 2600 g and the supernatant serum was recovered and stored at −80°C.

Compliance

Compliance was evaluated by face-to-face interviews and pill counting and confirmed by S-TxB$_2$ measurements. In order to optimise compliance, patients received a tablet dosage box with seven non-enteric coated aspirin tablets for the last 7 days before blood sampling.

Statistics

Continuous data are presented as mean±SD if data were normally distributed, as geometric mean with 95% CI if normally distributed when log-transformed, and as medians with interquartile range (IQR) if not. Unpaired data from two groups were compared by the two-sample t test if normally distributed and by the Mann−Whitney U test if not. Distributions of categorical

variables were compared with the χ^2 test and presented as absolute counts and percentages. Multiple linear regression was used to test the effect of PPI treatment on platelet aggregation adjusted for baseline characteristics. A two-tailed probability value of p<0.05 was considered statistically significant. CI were calculated at the 95% level. Statistical analyses were performed using GraphPad Prism version 5.0 and Stata version 9.0.

RESULTS

Baseline characteristics of the study population are shown in table 1.

Patients treated with PPIs did not differ with respect to demographic features and risk factors, except for an excess use of diuretics. The distribution of generic PPI variants is given in table 2.

Platelet aggregation was significantly higher in patients treated with PPIs (median 180 (IQR 119−312) vs 152 (84−226) AU*min, p=0.003) (figure 1). In a multiple linear regression analysis, the effect of PPIs on platelet aggregation remained significant after adjustment for age, sex, body mass index, smoking, concomitant drug treatment, previous myocardial infarction and diabetes mellitus (p=0.013).

Hirudinised blood samples were obtained from a minor part (n=115, 16 of whom were treated with PPIs) of the study population. These samples confirmed a significantly higher

Table 1 Baseline characteristics of the study population

Characteristics	Patients receiving PPIs (n=54)	Control patients (n=364)	p Value
Demographics			
Age, years†	67.0 (10.1)	67.2 (9.4)	0.88
Male subjects*	41 (75.9)	283 (77.7)	0.77
Risk factors			
Smoking*			0.96
Never	19 (35.2)	134 (36.8)	
Previously	23 (42.6)	148 (40.7)	
Today	12 (22.2)	82 (22.5)	
Family history of IHD*	22 (40.7)	177 (48.6)	0.28
Systolic blood pressure, mm Hg‡	137.2 (132.6−142.2)	141.8 (139.7−143.8)	0.11
Diastolic blood pressure, mm Hg‡	81.0 (78.0 to 84.2)	83.3 (82.1 to 84.5)	0.17
Body mass index, kg/m²‡	28.4 (27.2 to 29.7)	27.4 (27.0 to 27.8)	0.10
Diabetes*	21 (38.9)	99 (27.2)	0.08
Biochemistry			
Creatinine, μmol/l§	87.0 (72.0−106.0)	83.0 (72.0−99.8)	0.40
Platelets, 10⁹/l‡	238.0 (222.3 to 254.7)	227.3 (221.9 to 232.8)	0.18
Medical history			
Previous MI*	38 (70.4)	244 (67.0)	0.63
Previous PCI*	49 (90.7)	328 (90.1)	0.88
Previous CABG*	15 (27.8)	71 (19.5)	0.16
Previous stroke*	7 (13.0)	29 (8.0)	0.22
Medications			
Statins*	51 (94.4)	325 (89.3)	0.24
β Blockers*	40 (74.1)	270 (74.2)	0.99
ACE inhibitors*	30 (55.6)	156 (42.9)	0.08
AT-II receptor antagonists*	9 (16.7)	68 (18.7)	0.72
Calcium antagonists*	13 (24.1)	94 (25.8)	0.78
Diuretics*	34 (63.0)	121 (33.2)	<0.0001

*n (%), comparison made using χ^2 test.
†mean (standard deviation), comparison made using t test.
‡geometric mean (95% CI), comparison made using t test.
§median (interquartile range), comparison made using Mann−Whitney test.
ACE, angiotensin converting enzyme; AT-II, angiotensin 2; CABG, coronary artery bypass grafting; IHD, ischaemic heart disease; MI, myocardial infarction; PCI, percutaneous coronary intervention; PPIs, proton pump inhibitors.

Table 2 Distribution of generic PPI variants among patients treated with PPIs (n=54)

Generic drug	Patients, n (%)
Pantoprazole	29 (54)
Omeprazole	5 (9)
Esomeprazole	12 (22)
Lansoprazole	8 (15)

PPIs, proton pump inhibitors.

platelet aggregation in patients receiving PPIs (geometric mean 284 (95% CI 201 to 401) vs 158 (135 to 185) AU*min, p=0.007).

Platelet activation was assessed by sP-selectin as shown in figure 2. Patients treated with PPIs had significantly higher sP-selectin levels (median 88.5 (IQR 65.2−105.8) vs 75.4 (60.0−91.5) ng/ml, p=0.005), indicating an increased extent of platelet activation. The effect of PPIs on platelet activation remained significant after adjustment for age, sex, body mass index, smoking, concomitant drug treatment, previous myocardial infarction and diabetes mellitus (p=0.013).

All patients returned empty pill boxes and claimed to be adherent to aspirin treatment. All patients demonstrated S-TxB$_2$ levels (geometric mean 0.96 (95% CI 0.88 to 1.05), range 0.04−18.18 ng/ml) far below the normal range of 327±123 ng/ml in healthy subjects not receiving aspirin[17] and well below 30 ng/ml, corresponding to a more than 95% inhibition of platelet COX-1 activity.[22] Patients treated with PPIs had significantly higher S-TxB$_2$ levels than patients not receiving PPI treatment (geometric mean 1.29 (95% CI 0.96 to 1.72) vs 0.92 (0.84 to 1.01) ng/ml, p=0.01).

DISCUSSION

This study is the largest to investigate platelet aggregation in patients receiving aspirin and concomitantly treated with PPIs. We evaluated the platelet aggregation and platelet activation in 418 fully compliant patients with CAD treated with non-enteric coated aspirin and no other antithrombotic drugs. Our main finding was a significantly higher platelet aggregation in patients treated with PPIs, who also demonstrated an increased extent of platelet activation as compared with patients with CAD not treated with PPIs.

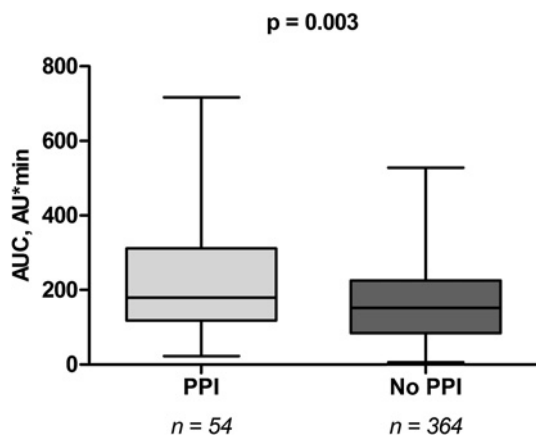Animal studies have shown that omeprazole reduces the analgesic and antipyretic effects of aspirin, which is probably

Figure 1 Platelet aggregation assessed by Multiplate. Platelet aggregation (median, IQR, range) in 418 patients with coronary artery disease: 54 patients receiving PPIs and 364 patients not receiving PPIs (no PPI). AU, aggregation unit; AUC, area under the aggregation curve; IQR, interquartile range; PPIs, proton pump inhibitors.
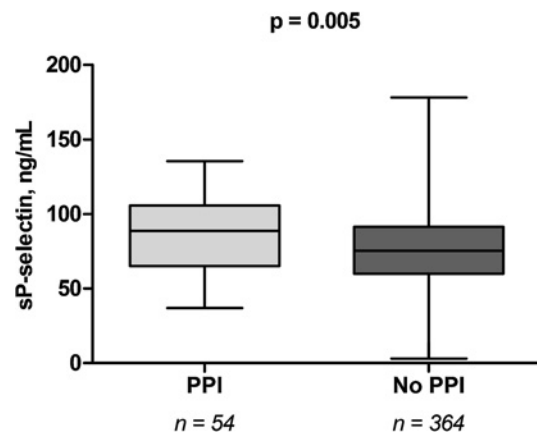

Figure 2 Platelet activation assessed by sP-selectin. sP-selectin levels (median, IQR, range) in 418 patients with coronary artery disease: 54 patients receiving PPIs and 364 patients not receiving PPIs (no PPI). IQR, interquartile range; PPIs, proton pump inhibitors; sP-selectin, soluble serum P-selectin.

attributable to the reduction in gastric aspirin absorption.[8 11] Similar findings were reported from a study performed on humans.[23] However, no reduction in the antiplatelet effect of aspirin was observed when administered concomitantly with either omeprazole 20 mg/day[24] or lansoprazole 30 mg/day.[25] We investigated the aspirin−PPI drug interaction in a clinical setting and observed a substantially higher residual platelet aggregation and platelet activation in patients treated with PPIs.

The higher aspirin dose used in the study by Inarrea et al (125 mg/day) might partly explain why their results differ from ours.[24] Hypothetically, dose increments might result in a slightly increased passive diffusion rate across the gastric mucosal membrane despite the elevation in pH caused by PPIs. In that case, the likelihood of detecting a difference using an aspirin dose of 125 mg is obviously reduced. A dose of 75−100 mg is the generally accepted choice for secondary prevention in Europe.[26]

In our study, a non-enteric coated formula of aspirin was used. In contrast, Adamopoulos et al used a coated formula when investigating a potential aspirin−lansoprazole drug interaction.[25] The lower bioavailability of the coated formula might explain why no difference between study groups was observed. The higher bioavailability of the non-enteric coated formula used in our study might amplify the measurability of the aspirin−PPI drug interaction, thus allowing us to demonstrate the inhibiting effect of PPIs on the antiplatelet effect of aspirin.

At present, a possible drug interaction between clopidogrel and PPIs is the focus of intense debate. Recent studies suggest that a class effect of PPIs on the antiplatelet effect of clopidogrel does not exist.[13 27] This might be attributable to differences in the inhibitory potency towards CYP2C19. In particular, pantoprazole seems to interfere little, if at all, with the metabolism of clopidogrel.[13] Since all PPIs affect gastric pH to roughly the same extent,[28 29] the aspirin−PPI drug interaction is likely to represent a class effect of PPIs.

Metabolism of another PPI, lansoprazole, depends partly on the CYP3A4 isoenzyme.[29 30] Aspirin is also to some extent metabolised by hepatic phase I reactions driven by CYP3A4.[31] This prompted Adamopoulos et al to investigate a potential drug interaction between lansoprazole and aspirin.[25] They performed a crossover study that did not confirm any CYP3A4-dependent aspirin−lansoprazole drug interaction.[25] Thus, the aspirin−PPI drug interaction observed in our study might be interpreted as a pH-dependent phenomenon related to changes in the

bioavailability and therapeutic activity of aspirin, rather than a question of competitive CYP inhibition.

Multiplate aggregometry was performed on citrated blood in all patients as well as on hirudinised blood in a subgroup of patients (n=115, 16 of whom were treated with PPIs). Hirudin, a selective thrombin inhibitor, has been suggested as an appropriate alternative to citrate owing to the undesirable Ca^{2+}-chelating properties of the latter.[32] In patients treated with aspirin, we found a significantly higher level of platelet aggregation in patients receiving concomitant PPI treatment measured both in citrated and in hirudinised blood. In line with previous findings, platelet aggregation was more potently inhibited under citrate preservation, which might result from the acidification and Ca^{2+} chelation caused by citrate.[33] Platelet aggregation was induced by arachidonic acid, which activates platelets specifically through the COX-1 pathway.

In clinical practice, a reduced response to aspirin is often explained by non-adherence to treatment.[34] In our study, all patients were fully compliant, but the patients with increased platelet aggregation had higher S-TxB$_2$ levels. This finding might suggest that even beyond the 95% level of COX-1 inhibition, platelet aggregation is affected by the actual level of COX-1 inhibition. S-TxB$_2$ is regarded as the most specific test for measuring the inhibitory effect of aspirin on platelets.[17 18]

Limitations

The design of our study did not allow any firm conclusions to be drawn on the potential causality between PPI treatment and aspirin response. Furthermore, we did not assess platelet aggregation after withdrawal of aspirin treatment, as this was considered unethical. Thus, we do not know if underlying platelet hyper-reactivity itself accounts for the higher platelet aggregation in patients treated with PPIs. Whole blood aggregometry might have potential drawbacks such as platelets interacting with other whole-blood elements potentially bypassing the platelet inhibition by aspirin.[35] Moreover, platelet aggregometry inherently requires ex vivo anticoagulation, which might affect platelet aggregability.[33]

CONCLUSIONS

Patients with CAD treated with PPIs had a reduced response to aspirin, as shown by increased residual platelet aggregation and platelet activation, compared with patients with CAD not taking PPIs. Concomitant use of aspirin and PPIs might leave patients at an increased risk of thrombotic events. These findings may affect the clinical practice of antithrombotic treatment. In view of the widespread use of PPIs, a randomised double-blind crossover study (PPI vs placebo + aspirin) is needed to explore further the inhibitory effect of PPIs on aspirin.

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