Does proton pump inhibitor reduce the antiaggregant efficacy of aspirin in ischemic stroke?

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Abstract

Objective: To evaluate the effect of using acetylsalicylic acid (aspirin) together with lansoprazole in the secondary prevention of ischemic stroke.

Materials and methods: 199 patients with a diagnosis of ischemic stroke and transient ischemic attack (TIA) using 100 mg aspirin regularly were included in the study. All patients were evaluated for the presence of aspirin resistance before starting the study. 57 patients with aspirin resistance were excluded from the study. The remaining 142 patients were divided into two groups: the 1st group consisted of those with stomach discomfort and the 2nd group consisted of those without stomach discomfort. Patients in group 1 were given 30 mg of lansoprazole taken before breakfast in addition to aspirin therapy. All patients were re-evaluated for the presence of aspirin resistance at a one-month follow-up. The antiaggregant activity was evaluated by the impedance aggregometry method in both groups.

Results: Of 142 patients, 75 were in group 1, and 67 were in group 2. There was no difference between the two groups in terms of age and gender distribution of vascular risk factors. There was no statistically significant difference between the two groups in terms of aspirin efficacy. The dose of aspirin was increased in patients with aspirin resistance (AR).

Conclusion: The combination of 30 mg lansoprazole and 100 mg aspirin does not cause a decrease in antiaggregant activity in the early period, but chronic use was not evaluated in this study. Patients with AR may benefit from an increase in the dose of aspirin.

Keywords: Aspirin, proton pump inhibitors, aspirin resistance, ischemic stroke, transient global amnesia

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INTRODUCTION

Stroke is the second leading cause of death after coronary heart disease among people aged over 60 worldwide and a leading cause of disability [1]. Besides the management of risk factors, drug prophylaxis plays an important role in the primary and secondary prophylaxis of stroke. Antiaggregant drugs, especially

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aspirin and clopidogrel have an established role and are used worldwide for the prophylactic treatment of stroke[2]. Despite their widespread utility gastrointestinal (GI) side effects are still a major reason for treatment discontinuation and gastrointestinal bleeding is a major fear when prescribing these drugs [3-7]. Treatment discontinuation puts the patients at risk of further cardiovascular events and increased mortality [8-10].

Proton-pump inhibitors (PPIs) are usually prescribed in addition to aspirin or clopidogrel in order to diminish GI side effects and risk of GI bleeding [11, 12]. Observation of increased coronary event rates in patients with concomitant use of clopidogrel and PPIs and following pharmacological studies raised concern about a reduced antiaggregant effect of this combination and a warning from regulatory authorities was issued in 2009 discouraging combined use of clopidogrel and PPIs [13]. Following this concern about clopidogrel, the same question has also been proposed for the combined use of aspirin and PPIs. Studies on the interaction of aspirin and PPIs are not as numerous as for clopidogrel and they have revealed conflicting results [14-19].

We aimed to assess the effect of adding lansoprazole, a PPI, to low-dose aspirin on the antiaggregant properties of aspirin in patients on secondary prophylaxis for stroke/TIA.

METHODS

Patients who attended the Akdeniz university department of neurology between January 2011 and January 2013 with the prior diagnosis of ischemic stroke or transient ischemic attack (TIA) and were already using aspirin 100 mg for stroke prophylaxis were enrolled into the study. Participants were informed about the study and informed consented. The study was approved by the Akdeniz university local ethical committee. Exclusion criteria were need for any other antiaggegant or anticoagulant medication other than aspirin; history of gastrointestinal bleeding; known history of allergic reactions towards the study drugs; family or personal history of bleeding disorders or hematological malignancies; major surgical procedure within 1 week before enrollment; regular use of any non-steroidal anti inflammatory drugs, antacids, proton pump inhibitors or any other drugs aiming at gastric overacidity; platelet count <150.000/ml or >450.000/ml, hemoglobin <8 g/dl.

All patients were evaluated for the presence of aspirin resistance prior entering the study. Patients with aspirin resistance were excluded. All patients were questioned about the presence of symptoms of gastric dyscomfort and patients were divided into two groups: Group 1 consisted of patients with gastric dyscomfort and Group 2 consisted of patients without gastric dyscomfort. All patients continued to receive 100 mg of aspirin taken after breakfast in the morning. Patients in group 1 were additionally given 30 mg of lansoprazol taken before breakfast. Patients were followed-up for one month and patient compliance was monitored by counting the empty drug blisters. All patients were re-evaluated for the presence of aspirin resistance on one month follow-up. Patients in both groups in whom aspirin resistance was detected were instructed to raise the aspirin dosis to 300 mg and were re-evaluated after another month. If aspirin resistance was still present the patient was switched to an alternative treatment.

Antecubital blood samples were taken into hirudin blood collection tubes in the morning hours from 08:00-11:00, within 30 minutes-2 hours after the patients took their aspirin dose. Patients had been using aspirin for at least 2 months prior to testing. Analysis of platelet function was performed using the Multiplate platelet analyzer (Dynabyte, Munich, Germany), a whole blood impedance aggregometer.

For the tests, 300 µl of hirudinized whole blood, placed in 300 µl of saline stored at 37°C, was incubated for 180 seconds. Then, 20 µl of arachidonic acid and TRAP agonists to be used during the test were separately placed into the cuvettes and the test was started. Results were obtained based on the Area Under Curve (AUC) after a six-minute measurement period. Each blood sample was analyzed within 5-30 minutes of collection. There were 5 test cells in the device and 2 independent sensor units in each test cell. The system works on the principle of increased electrical impedance between the two sensor wires caused by the activation of platelet adhesion and aggregation. Arachidonic acid (AA) (ASPItest, 0.5 mM) was used for initiation. The increased impedance caused by platelet aggregation on the sensor wires was recorded for 6 minutes. Data from the aggregation of platelets on

the sensor wires were converted to units labeled “AU”. The transformed data were then plotted as an aggregate curve plot against time. The area under the summing curve was labeled AUC. AUC >440 was defined as 'biochemical aspirin resistance'.

The statistical analysis was carried out by using SPSS 13.0 (Statistical Package for Social Sciences). To define the sample, continuous variables were expressed as mean ± standard deviation, median, and categorical variables as number and percentage. In cases where parametric test assumptions were provided, two independent group differences were analyzed by Independent Sample T-Test, and in cases where parametric test assumptions were not provided, non-parametric alternative of this test Mann-Whitney U Test was used. A p value < 0.05 was used to assess the sig-nificance for all statistical analyses.

RESULT

A total of 199 patients consented to participate in the study. Fifty-seven patients were excluded from the study because aspirin resistance was detected on the first test prior to the start of the study. Those patients were offered alternative treatment options. Of the remaining 142 patients 75 stated to have dyspeptic complaints on questioning and were started on lansoprazole 30 mg and formed group 1 while the 67 patients with no gastric complaints formed group 2. Age and gender distribution and demographics of the patients are given in Table 1. There was no difference in age and gender distribution nor vascular risk factors between both groups. After one month of follow-up all patients in group 1 reported to have no remaining dyspeptic complaints. After testing 5 (6,6%) patients in group 1 and 9 (13,4%) patients in group 2 were found to have developed aspirin resistance. The difference between both groups was found to be non-significant. In those patients who were found to have developed aspirin resistance the aspirin dose was raised to 300 mg(day). After another month of follow-up aspirin resistance was shown to have reversed in 1/5 (20%) of patients in group 1 and 5/9 (55,5 %) of patients in group 2. Due to the very small numbers the difference between both groups was found to be non-significant.

DISCUSSION

Meta-analyses have shown that patients who take aspirin for the prevention of cardiovascular disease have a

Table 1: Baseline characteristics and Aspirin Resistance (AR) of group 1 and group 2.

	Grup 1 (Aspirin+PPI) (n=75)	Grup 2 (Aspirin) (n=67)	p
Age (years) mean±SD	57.45±8.9	58,51±11.5	ns
Gender (female/male)	37/38	30/37	ns
History of diabetes mellitus n (%)	3 (2.1)	12(8.5)	ns
History of hypertension n (%)	16 (11.3)	12(8.5)	ns
Heart disease n (%)	23 (16.2)	21 (14.8)	ns
Smoking n (%)	18 (12.7)	13 (9.2)	ns
Hyperlipidemia n (%)	15 (10.6)	16 (11.3)	ns
Duration of aspirin use months mean±SD	2.2 ±1	2.1±0.9	ns
Infarct n (%)	11 (5.5)	13(6.5)	ns
Lacunar infarct n (%)	30 (15,1)	10 (5)	ns
TIA n (%)	34 (17.1)	41 (20.6)	ns
30th days AR n	5 (5/75)	9 (9/67)	ns
60TH days AR n	1 (1/5)	5 (5/9)	ns

*PPI: Proton Pump Inhibitors **AR: Aspirin Resistance ***TIA: Transient ischemic attack

P <0.05 =S (Significant)

P >0.05= NS (Not significant)

1,7-2,5 times higher risk of gastrointestinal bleeding when compared to controls even when given in low doses [3, 4]. The use of enteric-coated aspirin tablets does not alter the risk of GI bleeding when compared to plain aspirin [20-23]. To reduce the risk of GI bleeding associated with aspirin a common practice is to add gastric acid-reducing agents to the treatment. Proton pump inhibitors are the preferred choice due to their proven efficacy in reducing aspirin-related GI symptoms [12, 24-26]. Even the utility of combined preparations of aspirin and a PPI has been suggested in order to increase drug compliance [27, 28].

A warning from regulatory authorities discouraging combined use of clopidogrel and PPIs in 2009 following observation of increased coronary event rates in patients using this drug combination triggered a multitude of pharmacological studies assessing this issue and brought together the question and concern whether the same could be extrapolated to aspirin [13, 29]. Even though the interactions between clopidogrel and PPIs have been reported in numerous studies, research on the potential role of PPIs on platelet aggregation when combined with aspirin has been limited [14-19].

Aspirin is absorbed across the gastric mucosal membrane and needs an acidic environment for bioavailability [30]. PPIs raise the gastric PH by inhibiting acid secretion from gastric parietal cells [31] and have been shown to reduce the gastric absorption of aspirin [30, 32].

Omeprazole has been shown to decrease the levels of and reduce the analgesic and antipyretic effects of aspirin in experimental studies [32, 33]. Würtz et al showed that the addition of a PPI to 75 mg of non-enteric coated aspirin lead to a significant drop in antiagregant function as demonstrated by platelet aggregometer and significantly higher sP-selectin and S-TxB2 levels [14]. More than half of the patients in that study were using pantoprazole, and only 15% were on lansoprazole. PPIs, but not H2 receptor antagonists, have been reported to increase cardiovascular mortality and morbidity 1,46 fold in a study on 19.925 patients with cardiovascular disease [15].

The results of our study are contradictory to the aforementioned studies. We found that in the secondary prophylaxis of stroke/TİA adding 30 mg of lansoprazole to a standard dose of 100 mg non-coated aspirin did not change the effect of aspirin on platelet functions after one month as measured by blood impedance aggregometry test and multiplate test. Similar results have been reported by others who have shown platelet functions to be unaltered when standard low doses of aspirin were combined with omeprazole, esomeprazole, or lansoprazole. [16-18]. In a study designed similar to ours, Adamopoulos et al showed that after one month of treatment the efficacy of 100 mg enteric-coated aspirin did not change when 30 mg of lansoprazole was added to the treatment [17]. The results of a large cohort study on more than 80.000 patients also demonstrated no difference in rates of non-fatal MI and cardiovascular death [19].

Looking at the results of these studies the interaction between aspirin and PPIs seems to be controversial. One of the reasons for these contradicting results may be that the aspirin dose in the study by Würtz et al was 75 mg/day, which is somewhat lower than the studies reporting no interaction with PPIs. This is also confirmed by our finding that increasing the dose of aspirin in those with aspirin resistance helped restoring the efficiency of aspirin. It is also possible that different PPIs might have different effects on the antiaggregant properties of antiplatelet drugs as has been shown for clopidogrel which is efficient in combination with pantoprazole and rabeprazole but not with other PPIs [34, 35]. In the study by Würtz et al, only 15% of patients were using lansoprazole and the majority was on pantoprazole [14]. Taking into account that studies that did not find a decreased treatment effect of aspirin+PPI mainly were conducted with other PPIs than pantoprazole, it could be possible that this might be a differentiating factor.

Aspirin is the mainstay of prophylaxis in the majority of cardiovascular and cerebrovascular diseases. Because of fear of gastrointestinal bleeding, low doses are preferred to high doses without any demonstrated compromise inefficiency [36, 37]. Although considered safer, it has been shown that the risk of gastrointestinal bleeding is substantial even with low doses of aspirin [3, 4]. Therefore gastric protection is important to protect patients from a potentially fatal side effect. On the other hand the drug added to aspirin should not be compromising its antiaggregant effect. We demonstrated that adding 30 mg of lansoprazole to 100 mg of non-coated aspirin is a safe combination and does not alter the effect of aspirin on platelet function.

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Conflict of interest

The authors declare that they have no conflict of interest.

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