Antiplatelet Activity of Clopidogrel was not Reduced by Long-term Coadministration of Atorvastatin Compared with Coadministration of Fluvastatin

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Abstract

Background : Recently there has been concern about the antiplatelet effect of clopidogrel which could be attenuated by atorvastatin due to shared enzyme in metabolism. However, recent reports showed concomitant short-term use of statins does not significantly inhibit antiplatelet activity of clopidogrel. We analyzed how two statins metabolized by different hepatic enzymatic pathway together with long-term use of clopidogrel affect platelet aggregation.

Methods : 98 patients prior to or after coronary artery stenting due to stable angina or acute coronary syndrome with hyperlipidemia and they were divided into three groups: Group1 (n=32, clopidogrel + pravastatin 40 mg) , Group2 (n=33, clopidogrel 75 mg daily + atorvastatin 10 mg [metabolized by cytochrome P450(CYP)3A4 daily], Group3 (n=33, clopidogrel 75 mg daily + fluvastatin 40 mg [metabolized by CYP2C9) daily]. All patients received aspirin and a loading dose of 300 mg of clopidogrel. Platelet aggregation was evaluated by two channel whole blood aggregometer in response to 5 μmol/L of adenosine diphosphate.

Results : Baseline characteristics show no significant statistical difference between three groups at 95% confidence interval. Antiplatelet activity was 52.8 $\pm$9.6% for before clopidogrel and were 26.4 $\pm$ 10.9%, 27.8 $\pm$ 10.5% and 30.9 $\pm$ 11.7% for pravastatin, fluvastatin and atorvastatin plus clopidogrel, respectively. There was no significant difference between the platelet aggregation of each combination group ($p > 0.05$), but comparing before clopidogrel to each of others ($p < 0.001$).

Conculsions : Our data suggest that platelet aggregation was not affected by long-term coadministration of clopidogrel and atorvastatin or fluvastatin.

Key words : Antiplatelet activity, Clopidogrel, Atorvastatin, Percutaneous coronary intervention

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Introduction

Clopidogrel is an important orally administered aniplatelet agent as an adenosine diphosphate (ADP) receptor blocker to prevent thrombosis after coronary artery stenting and is widely available in patients with acute myocardial infarction, atherosclerotic cerebral infarction and peripheral arterial disease approved by Food and Drug Administration (FDA).[1-6] Clopidogrel is an inactive thienopyridine prodrug and activated by cytochrome P-450 enzyme after oral intake.[7-9] Statins, 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, show significantly reducing risks of myocardial infarction, stroke, and cardiovascular death evidenced by large randomized trial of primary and secondary prevention of cardiovascular disease and their meta-analyses.[10] It is not uncommon simultaneous prescription of statins with clopidogrel metabolized by same hepatic P-450 enzyme (CYP3A4) to the patients of percutaneous coronary intervention (PCI) due to hyperlipidemia as a risk factor. With this same metabolic pathway there has been controversies after the report antiplatelet activity of clopidogrel could be attenuated by one of lipophilic statins (atorvastatin, simvastatin, lovastatin, etc) in patients undergoing coronary artery stenting complement.[11-13] Pravastatin is metabolized by sullfation and does not affect CYP substrates. In the present study, we tried to compare the change of antiplatelet activity of clopidogrel during long-term combination with either of two statins that has different hepatic enzymatic pathway.

Methods

We proceeded this study after taking informed consent from each patient and approval of institutional review board. Total 98 patietnts of stable angina or first episode of acute coronary syndrome (chest pain plus electrocardiographic changes and/or increased myocardial biochemical markers) and hyperlipidemia (LDL cholesterol level 〉 100 mg/dl measured within 24 hours from onset of symptoms) with coronary stenting patients were involved. None of the patients received statin before the study. Statin administration was started after the diagnosis of hyperlipidemia for all patients and nonrandomized and directed by the treating physicians. 32 patients were classified to group 1, for control, scheduled to taking loading dose of clopidogrel (300 mg) before 2 hours of PCI and continue the daily dosage of clopidogrel (75 mg) and pravastatin (daily 40 mg) after coronary intervention. Venous blood samples were drawn twice from this group, before loading and after 30 days of daily dosage of clopidogrel. From patients who already underwent PCI and received clopidogrel and atorvastatin or fluvastatin, we collected 66 patients who was appropriate to our inclusion criteria; clopidogrel plus atorvastatin (33 patients, group 2, daily 10 mg) and fluvastatin (33 patients, group 3, an equally efficient lipid lowering dose daily 40 mg). The duration of coadminstration was 157.4 ± 82.9 days for atorvastatin group and 174 ± 31.6 days for fluvastatin group at the sampling time. All patients had aspirin (100 mg) and a 300 mg loading and 75 mg daily maintenance dose of clopidogrel. For platelet anaysis, blood sample was taken from forearm vein then collected in 3.8% sodium citrate tube. Platelet aggregation was assessed within 2h from blood sampling. Ex vivo platelet aggregation was measured by using two channel Chrono-log whole blood aggregometer (Chrono-log corp. USA). Platelet rich plasma (PRP) was obtained as a supernatant after centrifugation of citrated blood at 1000 rpm for 10 minutes, then kept at 37 ℃ before use. The final platelet count was adjusted to 2 x 108 platelet/ml with autologous plasma. Platelet-poor plasma (PPP) was obtained by second centrifugation of blood fraction at 3500 rpm for 10

Table 1. Demographic and Clinical Characteristics of Patients

Characteristic	Clopidogrel + pravastatin (n=32)	Clopidogrel + Atorvastatin (n=33)	Clopidogrel + Fluvastatin (n=33)
Age, year	60.8 ± 11.7	58.9 ± 10.4	59.7 ± 11.5
Female gender, n(%)	11(34.3)	10(30.3)	11(33.3)
Body mass index, kg/m2	22.5 ± 5.9	23.9 ± 2.4	23.6 ± 2.5
Risk factors, n(%)			
Current smoking	7(21.9)	7(21.2)	6(18.2)
Hypertension	23(71.9)	24(72.7)	22(71.0)
Diabetes mellitus	7(21.9)	7(21.2)	8(24.2)
Stable Angina, n(%)	21(65.6)	22(66.7)	21(63.6)
Unstable angina, n(%)	7 (21.9)	7 (21.2)	8 (24.2)
Acute myocardial infarction, n(%)	4 (12.5)	4 (12.1)	4 (12.1)
Other medication, n(%)			
Aspirin	32(100)	33(100)	33(100)
Calcium channel blocker	16(50.0)	18(54.5)	17(51.5)
β-blocker	18(56.3)	20(60.6)	19(57.6)
ACE inhbitor	15(46.9)	17(51.5)	17(51.5)
Angiotensin receptor bloker	9(28.1)	9(27.3)	11(33.3)
Nitrates	9(28.1)	12(36.4)	11(33.3)
Diuretics	4(12.5)	6(18.1)	5(15.2)
Duration of clopidogrel and statin, day	34.2 ± 9.2	167.5 ± 72.6	171 ± 34.2

minutes. Maximal light transmission curve was assessed for 5 minutes after adding 5 μmol/L adenosine diphosphate (ADP) as measurement of platelet aggregation. PPP was a baseline as reference. We excluded the patients with active bleeding and bleeding diathesis, malignancies, oral anticoagulation therapy with coumarin derivate, recent treatment (less than 14 days) with a GP IIb/IIIa antagonist or a platelet count 〈 100 x 109/L. Additional exclusion criteria was applied to the patients with having medication with known CYP3A4 inducer or inhibitors except medicines on table.

Statistical analysis

Continuous variables are expressed as mean ±SD. One-way analysis of variance (ANOVA) was used for comparison for baseline parameters among the study groups. Categorical variables were compared using chi-square test. ANOVA, with Bonferroni correction for multiple comparisons, was used to multiple group comparisons of antiplatelet activity in the fig. 1. A probability value of 〈0.05 was considered significant. All statistical analyses were performed with SPSS version 12 software. The effective sample size for

each group to give a power of 0.80(α = 0.05, estimated effect size = 0.1) is 30.

Results

Demographic and clinical characteristics of patients are indicated in Table 1. There were no differences in age, sex, body mass index, cardiovascular risk factors (hypertension, diabetes mellitus, current smoking) (Table1). Antiplatelet activity was 52.8 ± 9.6% for before clopdogrel and were 26.4 ± 10.9%, 30.9 ± 11.7%, 27.8 ± 10.5% for pravastatin, atorvastatin and fluvastatin plus clopidogrel. The difference of 5 μmol/L ADP -induced platelet aggregation between each combination group (pravastatin vs atorvastatin, pravastatin vs fluvastatin, atorvastatin vs fluvastatin) were 0.09, 0.63 and 0.17 and comparing before clopidogrel to each of others (vs pravastatin, vs atorvastatin and vs fluvastatin plus clopidogrel) were 〈0.001 for all on p value with 95% confidence interval(Fig. 1).

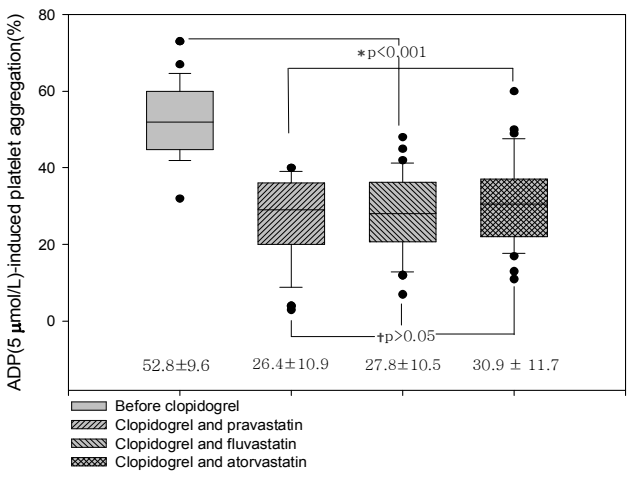

Figure 1.

Fig. 1. Antiplatelet activity of clopidogrel is not significantly influenced by atorvastatin or fluvastatin with long-term coadministration. The number shows each mean value. * before clopidogrel versus each of three others. versus between three mean values. Boxes represent the middle 50% of values and are crossed by median line. The whiskers represent the interquartile range. Outliers are represented as dots.

Comparison of each character between three groups does not show significant statistical difference at 95% CI.

Discussion

The results of the present study can propose that the coadministration of atorvastatin (metabolized by cytochrome P450(CYP)3A4) or fluvastatin (metabolized by CYP2C9) with clopidogrel in patients with stable angina or first episode of acute coronary syndrome for long-term duration does not significantly affect the antiplatelet acivity of clopidogrel. Recent studies reported that the coadministration of statins that are CYP3A4 substrates with clopidogrel may competitively inhibit the metabolic activation of clopidogrel in the liver and provided controversial results as to whether short-term therapy with clopidogrel in conjunction with atorvastatin could attenuate the antiplatelet efficacy of clopidogrel.[12,13] It has raised a number of concern about the possibility of any specific deleterious interaction between clopidogrel and statins. However, data from a post-hoc analysis of the Clopidogrel for Reduction of Events during Observation (CREDO) trial showed that there is no adverse effect on the 28-day or 1-year composite clinical end points with clopidogrel and statin coadministration. Similarly, the results of the prospective Maximal Individual TheRapy of Acute myocardial infarction PLUS (MITRA PLUS) registry demonstrated that there was no significant difference between atorvastatin therapy and other statin therapies over a follow-up period of 14 months in the clinical outcomes of patients receiving clopidogrel therapy.[14,15] Furthermore, the Interaction of Atorvastatin and Clopidogrel Study (Interaction Study) showed that atorvastatin does not affect

the platelet biomarkers after clopidogrel administration, compared with other statins or no statin, within 24 hours in patients with undergoing coronary stenting.[16] Mitsios et al. reported that the therapeutic efficacy of clopidogrel in patients with ACS is not significantly influenced by the concomitant administration of atorvastatin for 5 weeks, and clopidogrel does not affect the therapeutic efficacy of atorvastatin.[17] Also, Mukherjee et al. reported that there was no significant difference in clinical benefit between a CYP3A4 statin and a non-CYP3A4 statin when used in conjunction with clopidogrel.[18] Altogether, these results including ours may suggest that the adverse interaction in platelet function is probably an ex vivo phenomenon and may not be significantly relevant in clinical practice. Consequently, our results could provide suggestion that statins does not influence the antiplatelet effect of clopidogrel during the long-term co-administration (the mean duration; 157.4 ± 82.9 days), and may support a basis as to there was no significant difference in clinical benefit between a CYP3A4 statin and a non-CYP3A4 statin with concomitant clopidogrel long term use. Our study has several limitations: a small scale study without clinical outcome and the lack of randomization between patients with atorvastatin and fluvastatin therapy and the measurement of platelet aggregation not accompanied with in vivo test and only 5 μmol/L ADP-induced platelet aggregation and inclusion of only basal dosage of atorvastatin. Therefore, the further study for the clopidogrel dependent platelet inhibition in accordance with increment of dose of lipophilic statin and more of ADP stimulation dose might be needed.

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