Effect of 150-mg vs 300-mg Loading Doses of Clopidogrel on Platelet Function in Japanese Patients Undergoing Coronary Stent Placement

Kenichi Fukushima, MD; Yoshio Kobayashi, MD; Hideki Kitahara, MD; Yo Iwata, MD; Takashi Nakayama, MD; Nakabumi Kuroda, MD; Masayuki Ooyama, MT*; Fumio Nomura, MD*; Issei Komuro, MD

Background  The loading dose of ticlopidine is 500 mg in both the US and Europe and 200 mg in Japan. A lower loading dose of clopidogrel might achieve adequate platelet inhibition in Japanese patients.

Methods and Results  Platelet aggregation was serially measured at baseline, and 2, 4, 6, and 8 h after 150-mg (n=20) and 300-mg (n=20) clopidogrel loading. Platelets were stimulated with 5 and 20 μmol/L adenosine diphosphate (ADP) and aggregation was assessed by optical aggregometry. Pretreatment ADP-induced platelet aggregation in the 150-mg clopidogrel group did not differ from that of the 300-mg group. The administration of 300 mg clopidogrel loading dose resulted in lower platelet aggregation 2 h after the administration (5 μmol/L ADP: 53±9% vs 61±12%, p<0.05 and 20 μmol/L ADP: 61±10% vs 68±9%, p<0.05). A lower platelet aggregation induced with 20 μmol/L ADP was still observed 4 h after the 300-mg clopidogrel loading (58±10% vs 65±9%, p<0.05).

Conclusions  The 150 mg clopidogrel loading does not achieve rapid platelet inhibition. The 300-mg loading dose should be used to suppress platelet function rapidly even in Japanese patients undergoing coronary stent placement. (Circ J 2008; 72: 1282–1284)

Key Words: Antiplatelet therapy; Stent; Stent thrombosis

Faster platelet inhibition is achieved after the administration of a loading dose of clopidogrel compared to ticlopidine.1–3 The most widely prescribed clopidogrel loading dose in the US and Europe is 300 mg.2–4 The loading dose of ticlopidine is 500 mg in both the US and Europe and 200 mg in Japan.1,2 Thus, a lower loading dose of clopidogrel might be appropriate in Japanese patients. This study evaluated platelet function after the administration of 150-mg and 300-mg clopidogrel loading doses in Japanese patients undergoing coronary stent placement.

Methods

Patients  The ethics committee of Chiba University approved the study. Patients undergoing elective coronary stenting (n=40) were enrolled. The exclusion criteria were a history of bleeding diathesis, acute myocardial infarction within 48 h, cerebrovascular event within 3 months, malignancies, oral anticoagulation therapy with a coumarin derivate, other antiplatelet drugs except for aspirin, a platelet count <150×10^9/L, hematocrit ≤30%, a serum creatinine level >2.0 mg/dl, and liver disease resulting in a bilirubin level of >2.0 mg/dl. Patients gave written informed consent for participation. The present study was started when clopidogrel loading was off-label. There was no information about safety and efficacy of clopidogrel loading in Japanese patients. Thus, 150-mg clopidogrel loading was given to half of the patients (n=20) in consideration of safety. The other half of patients (n=20) received a 300-mg clopidogrel loading dose. In addition to the clopidogrel loading dose, each patient received 100 mg of aspirin.

A aggregometry  Peripheral venous blood samples were drawn from patients who were in a fasting state with a loose tourniquet through a short venous catheter inserted into a forearm vein. A multiple syringe sampling technique was used, and the first 2 ml of blood was discarded. Peripheral venous blood was collected in 3.8% citrate immediately before and then 2, 4, 6, and 8 h after the administration of a clopidogrel loading dose. Platelet aggregation was evaluated by optical aggregometry using a Whole-Blood Aggregometer (Chrono-Log, Haver Town, PA, USA). Platelet-rich plasma was prepared from citrated whole blood by centrifugation (500 g for 5 min). The final platelet count was adjusted to 200×10^9/L with autologous platelet-poor plasma. Platelets were stimulated with adenosine diphosphate (ADP) (5 or 20 μmol/L). Platelet aggregation was expressed as the maximal percentage change in light transmittance from baseline using platelet-rich plasma (0% light transmission) and platelet-poor plasma (100% light transmission) as references. Aggregation was recorded for 5 min. The analyzed parameter was maximal aggregation (%).
Table 1 Baseline Characteristics

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>150-mg (n=20)</th>
<th>300-mg (n=20)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female, n (%)</td>
<td>13 (15)</td>
<td>9 (12)</td>
<td>NS</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>65.3±14.4</td>
<td>66.3±17.2</td>
<td>NS</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>162.6±7.1</td>
<td>164.1±8.3</td>
<td>NS</td>
</tr>
</tbody>
</table>

Statistical Analysis

Statistical analysis was performed with StatView 5.0 software (SAS Institute, Cary, NC, USA). Continuous variables are expressed as mean±SD and categorical variables as frequency (%). Continuous variables were compared using the Student’s t-test. Categorical variables were compared with chi-square statistics. The difference in platelet function was evaluated by variance analysis for repeated measurements. P-values <0.05 was considered significant.

Results

Baseline clinical characteristics are presented in Table 1. Pretreatment ADP-induced platelet aggregation in the 150-mg clopidogrel group did not differ from the 300-mg group (Fig 1). Platelet aggregation induced with 5 and 20μmol/L ADP was suppressed after 150-mg (p=0.02 and p<0.01) and 300-mg clopidogrel loading (p<0.01 and p<0.01; Fig 1). However, 300-mg loading resulted in lower platelet aggregation 2h after the administration (5μmol/L ADP: 53±9% vs 61±12%, p<0.05 and 20μmol/L ADP: 61±10% vs 68±9%, p<0.05). A lower platelet aggregation induced with 20μmol/L ADP was still observed 4h after the 300-mg clopidogrel loading (58±10% vs 65±9%, p<0.05). There were no adverse events either in the 150-mg or 300-mg loading group.

Discussion

To the best of our knowledge, this is the first study demonstrating a time-course of platelet inhibition after the administration of clopidogrel loading in Japanese patients. Furthermore, the present study shows that substantial platelet inhibition is not achieved within the early hours after 150-mg clopidogrel loading.

With the exception of a few countries including Japan, clopidogrel plus aspirin has been the standard regimen after coronary stent implantation because side-effects of clopidogrel are less frequent compared to those of ticlopidine. Drug-eluting stent (DES) has significantly reduced in-stent restenosis. Late stent thrombosis after DES placement has emerged as a major concern. It is recommended that antiplatelet therapy should continue ≥12 months after DES implantation to prevent stent thrombosis. Thus, a favorable safety profile of clopidogrel is more important in the DES era. However, clopidogrel had been unavailable in Japan until May 2006 and, since then, on-label for only those patients who have suffered a thrombotic stroke. Long-term use of ticlopidine had been one of the limitations of DES in Japan. Finally, clopidogrel has been on-label for patients with acute coronary syndrome who undergo percutaneous coronary intervention (PCI), since October 2007.

Another benefit of clopidogrel is faster platelet inhibition after the administration of a loading dose of clopidogrel. Since the introduction of antiplatelet therapy, the incidence of stent thrombosis has been reduced. However, it still occurs in up to 1% of treated patients, especially in the early days after the intervention probably because of delayed onset of antiplatelet agents action. It takes several days to achieve maximal effect of clopidogrel on platelet function in the absence of a loading dose. Thus, the loading dose of clopidogrel should be given, if achievement of effective
levels of antiplatelet therapy is not anticipated before PCI. The most widely prescribed clopidogrel loading dose in the US and Europe is 300 mg; however, efficacy of higher clopidogrel loading doses has been evaluated in the US and Europe. The loading dose of ticlopidine is 500 mg in both the US and Europe and 200 mg in Japan. Thus, some interventionalists might have an idea that significant platelet inhibition would be achieved using a lower loading dose of clopidogrel. It might be used, especially when only 25-mg clopidogrel tablets are available (12 tablets for 300-mg loading dose!). This study shows that rapid platelet inhibition is not achieved after the administration of a 150-mg clopidogrel-loading dose. Thus, we should use a 300-mg loading dose of clopidogrel to achieve adequate platelet inhibition rapidly, even in Japanese patients.

Study Limitations

There were some limitations in the present study. First of all, the sample size was small, although it is comparable to that in previous studies. Second, this is not a randomized trial. As we mentioned above, there was no information about clopidogrel loading. Thus, we examined the lower dose first in consideration of safety. Third, platelet aggregation was assessed until 8 h after clopidogrel loading. Finally, the 150-mg clopidogrel loading group was older and took Ca antagonists more frequently than the 300-mg loading group. However, there are no definite evidences to demonstrate the influencing antiplatelet effect of clopidogrel loading.

Conclusions

The present study shows a time-course of platelet inhibition after the administration of 150-mg and 300-mg clopidogrel loading doses in Japanese patients. The 150-mg clopidogrel loading dose does not achieve rapid platelet inhibition. The 300-mg loading dose should be used to suppress platelet function rapidly, even in Japanese patients undergoing coronary stent placement.

References