Escalation Regimen of Cilostazol for Acute Brain Infarction

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Abstract

Objective Several reports have indicated that cilostazol is effective in the prevention of recurrence after cerebral infarction. However, cilostazol is inferior in tolerability for the adverse events than other anti-platelet agents. The goal of this study was to determine whether cilostazol escalation oral administration affects its tolerability.

Methods One hundred sixty-eight patients hospitalized for brain infarction with cilostazol treatment in our stroke center from 2006 to 2008 were enrolled in this study. During this term, we had two teams in our center and used different regimens. One of which used 100 mg b.i.d. regimen of cilostazol (Standard group) and the other used 50 mg b.i.d. for the initial 4 days, followed by a dose of 100 mg b.i.d. of it (Escalation group). Patient’s information such as baseline characteristics, adverse events, were collected and statistically analyzed retrospectively.

Results Seventy-nine patients were enrolled in Standard group and 87 patients in Escalation group. Comparison between these groups demonstrated that Escalation group had fewer patients who discontinued treatment (p=0.001) and a lower incidence of headache (p=0.004).

Conclusion This type of dose escalation regimen of cilostazol may be superior to the standard regimen in tolerability.

Key words: antiplatelet therapy, cilostazol, escalation regimen, headache, palpitation, tolerability

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Introduction

Cilostazol, a phosphodiesterase type 3 (PDE3) inhibitor (1-3), increases the concentration of cyclic AMP in several cells and is approved worldwide for the indication of obstructive arteriosclerosis, and the secondary prevention of atherosclerotic brain infarction as an additional indication in several Asian countries. Several groups have reported the efficacy of cilostazol administration for prevention of recurrence (4, 5) and post-stroke syndrome as well as the prevention of pneumonia (6), and improvements of depression (7), and dementia (8) after lacunar and atherothrombotic cerebral infarction. Recently, it was reported that cilostazol may be superior to aspirin in efficacy of secondary stroke prevention (9) regarding its pleiotropic effects. However, cilostazol may be inferior in tolerability, as it causes adverse events, especially headaches and palpitations.

For some drugs, attempts have been made to address adverse events specific to initial treatment. For example, in the treatment of Parkinson’s disease dopamine agonists are recommended in escalation regimens, in order to reduce gastrointestinal adverse events (10, 11). Accordingly, if adverse events in the initial treatment of cilostazol can be reduced by altering the dosing regimen, it may be a great benefit for patients. The object of the present retrospective study was to determine whether cilostazol escalation regimen is effective in improvement of tolerability.
**Table 1. Baseline Characteristics of Patients**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Standard Group</th>
<th>Escalation Group</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>80</td>
<td>88</td>
<td>N.S. (0.896)</td>
</tr>
<tr>
<td>Male / Female</td>
<td>58 / 22</td>
<td>63 / 25</td>
<td>N.S. (0.079)</td>
</tr>
<tr>
<td>Age: mean±SD</td>
<td>70.0±9.48 years</td>
<td>67.1±11.08 years</td>
<td>N.S. (0.753)</td>
</tr>
<tr>
<td>Body weight: mean±SD</td>
<td>62.0±11.21kg</td>
<td>61.5±10.31kg</td>
<td>N.S. (0.952)</td>
</tr>
<tr>
<td>Length of hospital stay median (range)</td>
<td>19 days (5 to 55 days)</td>
<td>17 days (6 to 149 days)</td>
<td>N.S. (0.952)</td>
</tr>
<tr>
<td>m-RS at hospitalization (Number of patients)</td>
<td>0(26) 1(10) 2(22)</td>
<td>0(13) 1(15) 2(17)</td>
<td>p = 0.0098</td>
</tr>
<tr>
<td>m-RS at discharge (Number of patients)</td>
<td>0(37) 1(19) 2(14)</td>
<td>0(26) 1(30) 2(17)</td>
<td>N.S. (0.0610)</td>
</tr>
<tr>
<td>Number of excluded patients</td>
<td>1</td>
<td>1</td>
<td>N.S. (0.946)</td>
</tr>
</tbody>
</table>

* a: Pearson’s chi-square test, b: unpaired t-test, c: Wilcoxon signed-rank test, d: Mann-Whitney U-test

**Table 2. Results**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Standard Group</th>
<th>Escalation Group</th>
<th>p value *</th>
</tr>
</thead>
<tbody>
<tr>
<td>The rate of discontinued patients by any adverse events</td>
<td>22.8% (18/79)</td>
<td>5.7% (5/87)</td>
<td>p = 0.001</td>
</tr>
<tr>
<td>The incidence rate of headaches</td>
<td>20.3% (16/79)</td>
<td>3.4% (3/87)</td>
<td>p = 0.004</td>
</tr>
<tr>
<td>The incidence rate of palpitations</td>
<td>7.6% (6/79)</td>
<td>2.3% (2/87)</td>
<td>N.S. (0.106)</td>
</tr>
</tbody>
</table>

* Pearson’s chi-square test

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**Materials and Methods**

This study investigated whether cilostazol escalation regimen affects its tolerability, thereby reducing dropouts due to adverse events after the start of cilostazol treatment. Among 670 consecutive patients hospitalized in our Stroke Center in the period from May 2006 to August 2008, 168 patients were treated with cilostazol newly starting within 3 days after onset of arteriosclerotic brain infarction. All of them were enrolled in this study. In this term, one of two teams in our center used the usual dose regimen of cilostazol (100 mg b.i.d.), and the other used the escalation dose regimen of cilostazol (50 mg b.i.d. for the initial 4 days of treatments, followed by an increase to 100 mg b.i.d.) with consideration of its major adverse events. In addition, all patients were given sodium ozagrel as an intravenous injection antiplatelet for the first 4 days. The regimen was determined by the team which had the first contact with the patient at the first hospital visit. Finally, 80 patients were entered into the former group defined as Standard group, and 88 patients were entered into the latter group defined as Escalation group.

Patient information, such as baseline characteristics, adverse events in order to compare tolerability, and incidence of recurrences in follow-up term in order to compare efficacy was collected and statistically analyzed. The categorical data, the continuous valuable and the ordinal scale were assessed with Pearson’s chi-square test, unpaired t test, Wilcoxon signed-rank test, and Mann-Whitney U test, respectively. All analyses were conducted with JMP (ver.6.0.3; SAS Institute).

**Results**

Patients were classified to Standard group (n=79) and Escalation group (n=87). There was no significant difference in sex, age, body weight, the modified Rankin Scale (m-RS) at discharge, but, there was a significant difference in the m-RS at hospitalization between two groups (Table 1). The m-RS at hospitalization indicated that more severe patients were enrolled in the Escalation group, and we confirmed there was no difference in the rate of improvement. Significantly more patients discontinued cilostazol treatment due to adverse events in Standard group than Escalation group (p=0.001; Table 2). Compared by each adverse event, a significant group difference was observed in the incidence of headache (p=0.004; Table 2). But, there was no significant difference in incidence of palpitation (p=0.106; Table 2).

The day of onset of adverse events is also shown in Fig.1. In particular, we found that headache and palpitation were the main adverse events which occurred on day 1 or day 2 in both groups, and there was a large difference in the num-
Figure 1. Onset date of any adverse event in cilostazol treatment. The day of onset of any adverse events induced by cilostazol treatment is shown.

Figure 2. Onset date of headache induced by cilostazol treatment. The day of onset of headache induced by cilostazol treatment is shown. Headache as an adverse event occurred on day 1 or day 2 in both groups.

Discussion

This study showed that the dose escalation regimen of cilostazol contributes to reducing adverse events and improves its tolerability. Cilostazol inhibits PDE3 and increases the concentration of cyclic AMP in several cells and causes pleiotropic actions such as inhibition of platelet activation, vasodilation, anti-proliferation of vascular smooth muscle cell and improvement of endothelial cell functions. Cilostazol causes headache through vasodilation of brain blood vessels, and most headaches tend to disappear after several days. One of the main effects of cilostazol is vasodilation and cilostazol is thought to contribute to the improvement of the prognosis for patients suffering from brain in-
fraction through enhancing blood flow at acute stage of stroke. We found that most headaches occurred at the initial day of cilostazol treatment and that there was a significant difference in the incidence between the standard regimen and the dose escalation regimen in this study.

Palpitation is caused by a direct action of cilostazol to myocytes. We could show a tendency to decrease these adverse effects with dose escalation regimen, but failed to show significant differences. It is written in the American package insert of pletal® that cilostazol increased heart rate, myocardial contractile force, and coronary blood flow as well as ventricular automaticity, as would be expected for a PDE III inhibitor in dogs or cynomolgous monkeys, and that heart rate increased in a dose-proportional manner by a mean of 5.1 and 7.4 beats per minute in patients treated with 50 and 100 mg b.i.d., respectively. Thus, the present result on palpitation might be related to this dose-proportional effect of cilostazol on heart rate. However, this study was conducted at a single center, and it has a limitation on the number of entries.

The results in the follow-up term suggested that there are no differences in preventing the recurrences of stroke in two regimens. Additionally, the total recurrence incidence of brain infarction for 119 patients in this study was not higher than that of previous studies (CSPS (4) and CSPS II (9)), showing the effectiveness of cilostazol for the prevention of stroke.

It would be inappropriate to simply assume the safety of this escalation regimen. The present dose escalation regimen may be useful for decreasing headache and discontinuities in the initial treatment with cilostazol, although much remains to be clarified.


References