Cilostazol to Overcome High On-Treatment Platelet Reactivity in Korean Patients Treated With Clopidogrel and Calcium-Channel Blocker

Young-Hoon Jeong, MD, PhD; Udaya S. Tantry, PhD; Kevin P. Bliden, BSc; Paul A. Gurbel, MD

Current oral antiplatelet therapy mainly targets the inhibition of cyclooxygenase-1 (COX-1) and the P2Y12 receptor in patients with acute coronary syndrome (ACS) and those treated with percutaneous coronary intervention (PCI). Despite proven clinical efficacy, the persistent ischemic event occurrence (~10%) suggests that dual antiplatelet therapy (DAPT) has reached a ceiling in its effect in attenuating thrombotic events and that some ischemic events are mediated by other pathways (non-COX-1 and non-P2Y12). However, the addition of inhibitors of the platelet thrombin receptor or coagulation factor to DAPT has not been clearly demonstrated to be effective in reducing ischemic event occurrence and has been associated with increased bleeding risk.

Phosphodiesterases (PDEs) are potential targets for inhibition to attenuate adverse cardiovascular events in patients with coronary artery disease (CAD). The platelet cyclic adenosine 3',5'-monophosphate (cAMP) and cyclic guanosine 3',5'-monophosphate (cGMP) stimulate protein kinases that are critical for regulating cellular function. PDEs convert cAMP and cGMP to inactive 5'-AMP and 5'-GMP, and influence downstream intracellular signaling. PDEs consist of 11 broad families (PDE1–PDE11), and their distribution and function differ according to species. Cilostazol is a dual inhibitor of PDE3 and adenosine reuptake that may have an important role in reducing ischemic events associated with CAD (Table 1). Cilostazol is a widely used selective and reversible inhibitor of PDE3, which is highly expressed in myocardial and vascular smooth muscle cells (VSMCs) and platelets. Cilostazol also inhibits adenosine reuptake into erythrocytes, endothelial cells, muscle cells, and platelets, thereby increasing interstitial and circulatory adenosine levels at clinically relevant concentrations (~3 μmol/L). Adenosine activates G-protein-coupled adenosine receptors, possesses a wide range of biological activities and influences cell survival through pre- and post-conditioning processes. In platelets and VSMCs, the interaction of adenosine with G-coupled adenosine A2 receptors results in increased intracellular cAMP. Thus, cilostazol can increase the production and also inhibit the breakdown of cAMP in platelets and VSMCs. In contrast, adenosine mainly acts on G-coupled adenosine A1 receptors in cardiac myocytes and reduces cAMP generation, which counteracts the cAMP elevation by PDE3 inhibition in the heart. This unique feature may contribute to the observed safety profile of cilostazol, and several studies have suggested a beneficial effect of cilostazol in arrhythmia prevention.

In this issue of the Journal, Lee et al provide more evidence regarding the benefit of adding cilostazol to DAPT (“triple antiplatelet therapy” [TAPT]) in reducing post-PCI clinical events. In the primary analysis of the CILON-T (influence of CILostazol-based triple antiplatelet therapy ON ischemic complication after drug-eluting stent implantation) trial, TAPT did not show superiority in reducing the composite of adverse cardiovascular outcomes after drug-eluting stent implantation despite greater reduction in platelet reactivity assessed by the VerifyNow P2Y12 assay (~45 P2Y12 reaction units [PRU]) compared with DAPT. In the current post hoc analysis of the CILON-T trial, the investigators divided the cohort into 4 groups based on calcium-channel blocker (CCB) prescription and the type of antiplatelet therapy in a 2×2 factorial manner. A significantly greater level of platelet reactivity at discharge was observed in patients treated with CCB and DAPT together compared with DAPT alone (251 vs. 226 PRU; P=0.008), but not in patients treated with TAPT (215 vs. 203 PRU; P=0.294). The composite of cardiac death, non-fatal myocardial infarction and ischemic stroke at 6 months post-PCI was increased in patients treated with CCB in the DAPT group (4.9% vs. 0.9%, P=0.016), but not in the TAPT group (0% vs. 1.8%, P=0.346). CCB use without concomitant cilostazol use was a significant predictor of total thrombotic events, and the addition of cilostazol to DAPT was associated with reduced clinical event occurrence in patients taking CCB (P=0.027 for thrombotic events). This analysis is consistent with earlier findings that adding cilostazol to DAPT following PCI may be beneficial in high-risk patients.

The current study findings are interesting and may be clinically relevant. The same investigators first reported that coadministration of the cytochrome P450 (CYP) 3A4 inhibitor may attenuate clopidogrel response and result in worsened clinical outcomes particularly in patients with the CYP2C19*2/*2 genotype. The latter observation is supported by the findings of the current study. Further support for this observation comes from

Table 1

<table>
<thead>
<tr>
<th>CILostazol-based triple antiplatelet therapy ON ischemic complication after drug-eluting stent implantation (ACS) and those treated with percutaneous coronary intervention (PCI).</th>
<th>Cilostazol</th>
<th>Clopidogrel</th>
<th>Calcium-channel blocker (CCB)</th>
<th>P2Y12</th>
<th>VerifyNow P2Y12 assay</th>
<th>Cardiovascular outcomes</th>
<th>P2Y12</th>
<th>VerifyNow P2Y12 assay</th>
<th>Cardiovascular outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>0%</td>
<td>1.8%</td>
<td>0.346</td>
<td>0.027</td>
<td>0.346</td>
<td>0.027</td>
<td>0.008</td>
<td>0.008</td>
<td>0.008</td>
<td>0.008</td>
</tr>
</tbody>
</table>

The opinions expressed in this article are not necessarily those of the editors or of the Japanese Circulation Society.

Received September 25, 2011; accepted September 25, 2011; released online October 5, 2011

Sinai Center for Thrombosis Research, Baltimore, MD (Y.-H.J., U.S.T., K.P.B., P.A.G.), USA; and Division of Cardiology, Department of Internal Medicine, Gyeongsang National University Hospital, Jinju (Y.-H.J.), Korea

Mailing address: Paul A. Gurbel, MD, Sinai Center for Thrombosis Research, Cardiac Catheterization Laboratory, 2401 W. Belvedere Ave, Baltimore, MD 21215, USA. E-mail: pgrabel@lifebridgehealth.org


All rights are reserved to the Japanese Circulation Society. For permissions, please e-mail: cj@j-circ.or.jp
a novel in vitro pharmacodynamic assay, which demonstrated that CYP3A4/5 isoenzymes play a significant role in both hepatic oxidation steps of clopidogrel. Among subjects homozygous for CYP2C19*2, Koreans displayed significantly lower CYP2C19 enzyme activity than Swedes (P<0.00001), which may imply that CYP3A4/5 enzyme activity plays a more important role in clopidogrel metabolism among Koreans.

The addition of cilostazol in PCI-treated patients has been shown to reduce major cardiovascular events such as mortality, myocardial infarction and stent thrombosis. Although the vasodilatory and antiproliferative effects of cilostazol have been proposed to explain its clinical benefit, a reduction in these ischemic events is unlikely to be explained by these mechanisms only. To date, several studies have demonstrated that adding cilostazol to DAPT significantly enhances platelet inhibition. Compared with double-dose clopidogrel therapy (150 mg/day), TAPT was associated with a greater decrease in adenosine diphosphate (ADP)-induced platelet aggregation. The latter observation has been consistently observed in various high-risk clinical settings (ACS, diabetes, and complex PCI), including the carriage of the homozygous for CYP2C19*2, Koreans displayed significantly increased PDE3-dependent (cAMP) activity. A significant increase in phosphodiesterase 3 (platelets, VSMC, heart, and adipocytes) activity implies that adenosine acts in platelets beyond its immediate influence on adenosine reuptake and platelet aggregation. This finding again supports the influence of adenosine on in vivo platelet aggregation. Taken together, it is important to note that the in vivo antithrombotic effect of cilostazol may not be completely reflected by the ex vivo platelet function test.

The interaction between cilostazol and CCB at the hepatic isoenzyme level cannot be overlooked. The decrease in platelet reactivity by the addition of cilostazol seems to differ between patients with and without CCB coadministration (at discharge: ≈37 vs. 22 PRU, and at 6-month: ≈52 vs. 41 PRU). Although cilostazol is a direct-acting drug, the 2 major metabolites of cilostazol, OPC-13015 (mainly produced by CYP3A4 and OPC-13213 (mainly produced by CYP3A5 and 2C19), account for approximately 50% of PDE3 inhibition. Single nucleotide polymorphisms (SNPs) of CYP2C19 and CYP3A5 thus may influence the pharmacokinetic and pharmacodynamic properties of cilostazol. Suri et al demonstrated that maximum plasma concentrations of cilostazol and OPC-13213 increased significantly, whereas OPC-13015 concentrations decreased significantly (all P<0.001), following erythromycin coadministration in healthy volunteers receiving cilostazol (Table 2). It has been demonstrated that OPC-13015 is 3-fold more potent in inhibiting platelet reactivity than cilostazol, whereas OPC-13213 is 3-fold less potent than cilostazol. Taking these findings together, CCB coadministration may moderately enhance the antiplatelet effect of cilostazol.

The current post hoc analysis by Lee et al has several limitations. A great body of data has demonstrated the reduced pharmacodynamic and clinical efficacy of clopidogrel in PCI-treated patients carrying the CYP2C19 loss-of-function allele.

---

**Table 1. Pharmacokinetics, Pharmacodynamics and Mechanisms of Cilostazol**

<table>
<thead>
<tr>
<th>Drug name</th>
<th>Chemical structure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cilostazol</td>
<td>6-[4-(1-cyclohexyl-1H-tetrazol-5-yl)butoxy]-3,4-dihydro-2(1H)-quinolinone</td>
</tr>
</tbody>
</table>

**Mechanism**
Inhibition of phosphodiesterase 3 (platelets, VSMC, heart, and adipocytes) → increased cAMP
Inhibition of adenosine uptake (erythrocytes, platelets, muscle cells, and endothelial cells) → increased adenosine

**Metabolism**
Extensively metabolized by liver
*OPC-13015: mainly produced by CYP3A4
*OPC-13213: mainly produced by CYP3A5 and 2C19

**Maximal concentration** 3–3.65 h
**Maximal effect** 6 h (platelet inhibition)
**Excretion** Urine (74%), feces (20%)

**Table 2. Pharmacokinetics of Cilostazol, and Its Active Metabolites Following Oral Administration of 100 mg Cilostazol Before and After Erythromycin Co-Administration**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Cilostazol</th>
<th>OPC-13015</th>
<th>OPC-13213</th>
</tr>
</thead>
<tbody>
<tr>
<td>t&lt;sub&gt;max&lt;/sub&gt; (h)</td>
<td>4±2</td>
<td>5±3</td>
<td>7±3</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (μg/L)</td>
<td>621±172</td>
<td>886±198 (†47%)</td>
<td>129±39</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;t&lt;/sub&gt; (μg·h/L)</td>
<td>8,917±3,252</td>
<td>16,770±9,475 (†87%)</td>
<td>2,667±1,546</td>
</tr>
</tbody>
</table>

*Before After Before After Before After*

I<sub>max</sub>, time to reach maximum plasma concentration; C<sub>max</sub>, maximum plasma concentration; AUC<sub>t</sub>, area under the plasma concentration-time curve t.
Although demonstrating the relation of platelet reactivity to the occurrence of clinical events in patients receiving TAPT, the authors should have included the demographic variables, drug–drug interactions and SNPs as a combined variable. The investigators did not mention the time of blood sampling for platelet function measurement after the last-dose administration. In a healthy volunteer study using pharmacokinetic-pharmacodynamic model (a single dose of 100 mg cilostazol), peak cilostazol concentration was achieved at 3.65 h, but maximal platelet inhibition was at 6.05 h after cilostazol administration. The maximum pharmacodynamic effect was observed =8 h after clopidogrel loading. Because the pharmacodynamic effect of each drug in TAPT can vary, even during maintenance treatment, the specific sampling time may be important for reducing possible confounders. Finally, platelet reactivity was similar or increased after 6-month therapy compared with platelet reactivity measured at discharge. This is not in agreement with other pharmacodynamic studies in which a decrease in platelet reactivity (≈40 PRU) was reported. The current post hoc analysis has provided more insight regarding the potential benefits of adding cilostazol to DAPT, a strategy that may overcome the limitations of clopidogrel–drug interactions, enhance platelet inhibition, and reduce the occurrence of post-PCI ischemic/thrombotic events without an increase in bleeding risk. However, we must keep in mind that an ex vivo platelet function test alone may not completely reflect the pleiotropic effects of cilostazol therapy.

Acknowledgments
This study was partly supported by grants from Institute of the Health Sciences, Gyeongsang National University, Jinju, South Korea, and Sinai Hospital of Baltimore, Baltimore, MD, USA.

Disclosures
Conflict of Interests: Dr Jeong received honoraria for lectures from Sanofi-Aventis, Daiichi Sankyo Inc, and Otsuka. Dr Gurbel received research grants, honoraria, and consultant fees from Haemoscope, AstraZeneca, Schering-Plough/Merck, Medtronic, Lilly/Daiichi Sankyo Inc, Sanofi-Aventis/Bristol Myers, Portola, Boston-Scientific, Bayer, Novartis, Accumedics, Boehringer Ingehelm, and Johnson and Johnson.

References