

TOP Journal Club

Vol 8: Number 12 December 2005

Cilostazol, an Inhibitor of Type 3 Phosphodiesterase, Produces Endothelium-Independent Vasodilation in Pressurized Rabbit Cerebral Penetrating Arterioles.

J Vasc Res. 2005;11:86-94

We investigated the effects of cilostazol, a potent inhibitor of cGMP-inhibited cAMP phosphodiesterase, on mechanical activity of isolated pressurized rabbit cerebral penetrating arterioles with special reference to the function of the endothelium. Both cilostazol and milrinone, another inhibitor of cAMP phosphodiesterase, produced vasodilation of the cerebral penetrating arterioles in a dose-dependent manner. Pretreatment with selective inhibitors of cyclooxygenase or nitric oxide synthase, or chemical denudation of the endothelial cells caused no significant effect on the cilostazol-mediated vasodilation of the cerebral arterioles. A selective large-conductance calcium-activated potassium channel inhibitor, iberiotoxin, and a selective protein kinase A inhibitor, H-89, caused no significant effect on the cilostazol-mediated vasodilation. In the cerebral arterioles, low concentration (10^{-6} M) of cilostazol or milrinone caused a significant shift of the dose-vasodilatory response curve for adenosine to the left. These findings suggest that cilostazol produces vasodilation independent of the presence of the endothelium or activation of endogenous vasodilative prostaglandins, nitric oxide, calcium-activated potassium channel and protein kinase A. In conclusion, the vasodilator action of cilostazol may, in part, contribute to the beneficial effect of preventing lacunar cerebral infarction in patients with functional damage of the endothelium in cerebral penetrating arterioles.

Triple versus dual antiplatelet therapy after coronary stenting: impact on stent thrombosis.

J Am Coll Cardiol. 2005;46(10):1833

OBJECTIVES: We evaluated safety and efficacy of triple antiplatelet therapy with aspirin, clopidogrel, or ticlopidine and cilostazol after coronary stenting. **BACKGROUND:** Triple antiplatelet therapy might have beneficial effect to prevent thrombotic complications in patients undergoing coronary stenting. **METHODS:** Patients undergoing successful coronary stenting were divided into dual antiplatelet therapy (aspirin plus clopidogrel or ticlopidine, group I, n = 1,597) and triple antiplatelet therapy (aspirin plus clopidogrel or ticlopidine plus cilostazol, group II, n = 1,415) groups. The primary end point included death, myocardial infarction, target lesion revascularization, or stent thrombosis within 30 days. The secondary end point was side effects of study drugs, including major bleeding, vascular complication, hepatic dysfunction, and hematological complications. **RESULTS:** Multi-vessel stenting and the use of long stents were more prevalent in group II than in group I. The primary end point was 0.8% in group I and 0.3% in group II ($p = 0.085$). Stent thrombosis within 30 days was significantly lower in group II (n = 1, 0.1%) than in group I (n = 9, 0.5%; $p = 0.024$). The independent predictors of stent thrombosis were primary stenting (odds ratio [OR] 7.9, 95% confidence interval [CI] 2.0 to 30.8, $p = 0.003$) and triple therapy (OR 0.12, 95% CI 0.015 to 0.98, $p = 0.048$). The overall adverse drug effects, including major bleeding, neutropenia, and thrombocytopenia, were no different between two groups (1.8% vs. 2.6%, $p = 0.104$). **CONCLUSIONS:** Compared with the dual antiplatelet regimen, triple antiplatelet therapy seemed to be more effective in preventing thrombotic complications after stenting without an increased risk of side effects. Triple antiplatelet therapy might be safely applied in patients or lesions with a high risk of stent thrombosis.

Cilostazol: Potential mechanism of action for antithrombotic effects accompanied by a low rate of bleeding.

Atheroscler Suppl. 2005 Nov 3

Treatment of thrombotic disease requires a delicate balance between prevention of new

thrombotic events and management of bleeding complications. Various antiplatelet and anticoagulant agents have been used to this end, with varying degrees of success. Among the antiplatelet agents tested so far, cilostazol, which selectively targets phosphodiesterase III (PDE-III), has unique features. Cilostazol is classified as an antiplatelet agent because it inhibits the platelet aggregation induced by collagen, 5'-adenosine diphosphate (ADP), epinephrine, and arachidonic acid. Unlike other antiplatelet agents cilostazol not only inhibits platelet function but also improves endothelial cell function. Platelets circulate throughout the body with continuous tethering on the surface of endothelial cells. When endothelial cells are stimulated, the number of activated, or pre-conditioned, platelets in circulation increases. These platelets enhance thrombus formation at the sites of endothelial disruption. Cilostazol effectively prevents the onset of thrombotic disease, not only by direct inhibition of platelet function, but also by reducing the number of activated or pre-conditioned platelets in circulation. Secondary prevention of stroke with modest increase in bleeding complications was achieved by administration of cilostazol in the Japanese Cilostazol Stroke Prevention Study done in Japan. These results suggest that cilostazol may reduce the risk of stroke without increasing the risk of bleeding complications.

Effect on platelet function of cilostazol, clopidogrel, and aspirin, each alone or in combination.

Atheroscler Suppl. 2005 Nov 3

Management of peripheral arterial disease (PAD) requires standard atherosclerotic risk management interventions. However, PAD is often complicated by walking pain (intermittent claudication [IC]), which requires symptom-specific therapies as well. Thus, all PAD patients are encouraged to take antiplatelet agents to reduce the associated risks of major cardiovascular events, and those with IC may also require treatment with cilostazol, an agent proven to increase exercise capacity and enhance quality of life in these patients. Although it was initially thought that cilostazol's antiplatelet

properties might render it unsafe to use in combination with other platelet inhibitors because of possible additive effects, a recent study has dispelled such concerns. There is evidence that in a crossover trial of 21 patients with PAD and IC, aspirin alone, or clopidogrel alone, significantly increased bleeding times, but cilostazol alone did not. The combination of aspirin and clopidogrel had a greater effect on increasing bleeding time than either monotherapy, and no further bleeding time prolongation was observed, when cilostazol was added to any aspirin/clopidogrel regimen. These findings suggest that PAD patients with IC may be safely managed with both cilostazol and standard antiplatelet therapy, without increasing the risk of adverse bleeding effects.

A scientific rationale for the CREST trial results: Evidence for the mechanism of action of cilostazol in restenosis.

Atheroscler Suppl. 2005 Nov 3

The Cilostazol for RESTenosis (CREST) clinical trial was initiated to evaluate the efficacy of cilostazol, an antiplatelet drug, in inhibiting restenosis after stent implantation in a native coronary artery as evaluated by quantitative coronary angiography. Preliminary results suggest that cilostazol reduces restenosis by nearly 40% over standard therapy alone. Restenosis after coronary stenting is primarily attributed to neointimal formation. Cilostazol decreases the activity of phosphodiesterase type 3, leading to the accumulation of cyclic adenosine monophosphate, which initiates a cascade of events including upregulation of anti-oncogenes p53 and p21 and upregulation of hepatocyte growth factor (HGF). The increase in p53 protein blocks cell cycle progression and induces apoptosis in vascular smooth muscle cells (VSMCs), leading to an antiproliferative effect. Upregulation of local HGF stimulates rapid regeneration of endothelial cells, which inhibits neointimal formation via two mechanisms: inhibition of abnormal VSMC growth and improvement of endothelial function. These mechanisms may be responsible for the improvement in restenosis shown in the CREST trial and a number of other trials in patients who

underwent percutaneous transluminal coronary angioplasty. These effects, in addition to antithrombotic and vasodilatory attributes of cilostazol, make it a potentially viable treatment option for preventing restenosis following coronary stenting.

The US experience with cilostazol in treating intermittent claudication.

Atheroscler Suppl. 2005 Nov 3

The management of peripheral arterial disease (PAD) patients with intermittent claudication (IC) requires both aggressive risk management and targeted symptomatic therapies. The phosphodiesterase inhibitor cilostazol is the only US Food and Drug Administration (FDA) approved medication to demonstrate consistent benefits on both objective measures of exercise capacity and subjective measures of everyday functioning and quality of life. Pentoxifylline is also approved by the FDA for the treatment of claudication, but with less clinical benefit than cilostazol. This report will provide an overview of cilostazol's role in the treatment of patients with IC. Data will be presented regarding the safety and efficacy demonstrated by cilostazol in clinical trials, as well as the effects of risk-factor control, exercise therapy, revascularization, and experimental drugs on the treatment of claudication in the PAD population. Based on the available evidence, a comprehensive approach to claudication management is recommended.

Cilostazol in secondary prevention of stroke: Impact of the Cilostazol Stroke Prevention Study.

Atheroscler Suppl. 2005 Nov 3

According to recent epidemiological data in Japan, stroke affects roughly 5.3 males and 3.9 females per 1000 person-years and is the third leading cause of mortality. At present, management strategies for secondary prevention of stroke include aggressive treatment of cardiovascular risk factors (i.e., hypertension, smoking cessation, etc.). Antiplatelet drugs in Japan, namely aspirin

and cilostazol, are utilized regularly for the prevention of secondary stroke. While aspirin is beneficial for a wide range of cardiovascular endpoints, including total and ischemic strokes, it is also associated with significantly increased risks for hemorrhagic infarction. Cilostazol, by contrast, has been shown to significantly reduce the risk of recurrent strokes without affecting the occurrence of intracranial hemorrhage. In the Cilostazol Stroke Prevention Study, a randomized double-blind, placebo-controlled trial involving more than 1000 Japanese patients, cilostazol was found to reduce the risk of secondary stroke by 41.7% compared with placebo, a statistically significant reduction ($P=0.015$). The greatest risk reduction (43.4% in cilostazol versus placebo, $P=0.0373$) was found in patients who initially had a lacunar infarction, suggesting that cilostazol has a specific effect against small-vessel disease. In addition, cilostazol achieved significant risk reductions on a number of combined endpoints (e.g., cerebral infarction, intracranial hemorrhage, myocardial infarction, or vascular death), and was associated with benefits in intent-to-treat analyses. These findings indicate that cilostazol may have a role as a vascular neuroprotectant, but the clinical implications are limited by the fact that patients were randomized to placebo instead of aspirin, which is standard of care.

Role of adjunct pharmacologic therapy in the era of drug-eluting stents.

Atheroscler Suppl. 2005 Nov 3

The success of percutaneous coronary intervention (PCI) has historically been limited by a relatively high rate of restenosis, a response of the coronary artery to trauma induced during PCI. Bare-metal stents, by providing a supportive intravascular scaffolding, have significantly reduced the incidence of restenosis compared with traditional balloon PCI. However, significant loss of lumen within the bare-metal device (in-stent restenosis) occurs in 10-30% of patients within 6 months of the procedure. The recent introduction of drug-eluting stents, permitting local delivery of high concentrations of immunosuppressive or anti-proliferative agents, promises to prevent the

processes underlying restenosis. Although these devices have been successful in providing an incremental reduction in rates of restenosis, they are expensive. To date, clinical trials of pharmacologic treatment have failed to demonstrate a clinically significant impact on restenosis. Recently, results of the Cilostazol for Restenosis (CREST) trial, a randomized, double-blind study, show that cilostazol reduces the risk of restenosis in patients who receive bare-metal stents, including high-risk patients. Effective adjunct pharmacologic therapy to prevent in-stent restenosis, therefore, remains desirable, particularly in patients receiving bare-metal stents, and potentially in patients receiving drug-eluting stents who are at high risk for restenosis (i.e., those with diabetes, long lesions, and small vessels).

[Resistance to antiplatelet drugs: current status and future research.](#)

[Expert Opin Pharmacother.](#) 2005;6(12):2027-45

Platelet reactivity and activation are important factors during the development of atherothrombotic processes and subsequent ischaemic complications. Pharmacological agents that suppress platelet function are proved to be the most efficient in the prevention and treatment of thrombotic complications. As the activation of platelets during thrombus generation involves many complex and redundant pathways, simultaneous use of different antiplatelet drugs that are directed against different targets have been effective in reducing adverse clinical events. The main antiplatelet drugs are aspirin (which inhibits thromboxane synthesis), thienopyridines (which block P2Y₁₂ receptors) and glycoprotein IIb/IIIa antagonists (which block glycoprotein IIb/IIIa receptors). In recent years, resistance or nonresponsiveness to antiplatelet therapy has been reported and, more importantly, are linked to the occurrence of adverse cardiovascular events. New treatment strategies to overcome nonresponsiveness are being sought. A focus on the development of simple, reproducible and user friendly point-of-care methods to determine aspirin/clopidogrel responsiveness should be

undertaken to assist clinicians in tailoring antiplatelet therapy to the individual patient.

[Role of disease status and type D personality in outcomes in patients with peripheral arterial disease.](#)

[Am J Cardiol.](#) 2005 Oct 1;96(7):996-1001

Patients with peripheral arterial disease (PAD) often experience diminishing quality of life (QOL) in many domains of their lives. However, factors associated with impaired QOL and perceived stress in these patients are not completely understood. The relative effects of disease status and type D ("distressed") personality (tendencies to experience negative emotions and be socially inhibited) on these patient-based outcomes were examined. It has been argued that type D personality might depend on disease status; therefore, its effect was examined in a combined sample of 150 patients with PAD and 150 healthy controls. The Type D Scale-14, World Health Organization Quality of Life Assessment Instrument-100, and Perceived Stress Scale-10 Item assessed type D personality, QOL, and perceived stress, respectively. PAD severity (mild, moderate, or severe) was not associated with QOL or perceived stress. However, patients with PAD reported decreased QOL ($p < 0.05$) compared with healthy controls. Type D patients reported significantly poorer QOL than non-type D patients across PAD and healthy subgroups ($p < 0.0001$). After controlling for disease status (presence or absence of PAD), type D personality remained associated with increased risk for impaired QOL (odds ratio [OR] 7.35, 95% confidence interval [CI] 3.39 to 15.96, $p < 0.0001$) and perceived stress (OR 6.45, 95% CI 3.42 to 12.18, $p < 0.0001$). Hence, type D personality was associated with impaired QOL beyond the impairment already related to PAD and with increased stress in this high-risk population. In conclusion, type D personality is not merely a function of PAD but seems to represent a different determinant of patient-based outcomes.

*<http://www.thai-otsuka.co.th/pxnews/index.html>
Dr. Shwe Win: shwewin@thai-otsuka.co.th*