

TOP Journal Club

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Endothelial Dysfunction & Cilostazol

Therapeutic potential of oral antiproliferative agents in the prevention of coronary restenosis.

The treatment of coronary artery disease has reached many milestones - from balloon angioplasty to drug-eluting stents. The last decade witnessed the revolution of bare metal stents with new designs, alloys and strut thicknesses. Yet restenosis, the aphorismic 'Achilles heel', remains to be conquered. The restenosis rates with balloon angioplasty alone are 30-40% and are reduced to 20-30% with stents. Although intravascular brachytherapy proved to be a durable and safely used technique to treat in-stent restenosis, clinical event rates were not reduced to single digits. Drug-eluting stents are showing positive results in this direction, but it is too early to predict their efficacy in various subsets of lesions. With the increased usage of these stents, there are reports of problems such as late stent malapposition, subacute and late thromboses, and aneurysm formations due to the vessel toxicity associated with this method of treatment. Furthermore, when multivessel stenting is considered, the cost of drug-eluting stents is a significant problem given the fact that these are no longer 'zero restenosis' devices. There is a definite need for a simple, safe and durable solution to restenosis. Oral agents are an alternative delivery strategy that can target multiple coronary lesions, which are targets for catheter-based revascularisation with any approved metal stent and with potentially lower cost. Although oral agents have been an interesting option to treat restenosis and several agents have been tested in trials since the 1980s, the results were disappointing. The development of devices such as intravascular ultrasound has led to a greater understanding of restenosis mechanisms, and the focus on pathophysiological mechanisms, which centred mainly on platelets, growth factors and lipids, has changed to inflammation, endothelium and smooth muscle cell proliferation. Accordingly, the targets of pharmaceutical agents have shifted from platelets to cell cycle inhibition, smooth muscle cell proliferation and migration, synthesis of extra cellular matrix, and inflammatory mediators. Initial encouraging results with oral drugs such as cilostazol, sirolimus (rapamycin) and thiazolidinediones indicate a definite place for this strategy to reduce restenosis. A desirable oral agent would be anti-inflammatory, inhibit smooth muscle cell migration and proliferation, promote endothelial growth, and be well tolerated and free from significant adverse effects. It may be useful to start with a high loading dose before stent implantation and then follow with a short-term lower maintenance dose. Future trials should be aimed at finding an ideal agent, effective loading dose, maintenance dose and optimum duration of therapy.

Drugs. 2004;64(21):2379-88.

Initial accumulation of platelets during arterial thrombus formation in vivo is inhibited by elevation of basal cAMP levels.

Platelet accumulation at sites of vascular injury is the primary event in arterial thrombosis. Initial platelet accrual into thrombi is mediated by interactions of platelet adhesion receptors with ligands on the injured endothelium or in the sub-endothelial matrix. The role of intracellular signals in initial platelet accumulation at sites of endothelial injury, however, is the subject of debate. We have used a newly discovered inhibitor of phosphodiesterase 3A (PDE3A) and the well-characterized PDE3A inhibitor, cilostazol, to modulate 3',5'-cyclic adenosine monophosphate (cAMP) levels in an in vivo model that enables the kinetic analysis of platelet accumulation. These studies demonstrate that elevation of basal cAMP levels results in an overall decline in platelet accumulation at the site of vascular injury. In particular, the initial rate of accumulation of platelets is inhibited by elevation of cAMP. Analysis of the kinetics of individual platelets at injury sites using intravital microscopy demonstrates that cAMP directs the rate at which platelets attach to and detach from thrombi. These studies demonstrate that cAMP in circulating platelets controls attachment to and detachment from sites of arteriolar injury. Thus, the status of the intracellular signaling machinery prior to engagement of platelet receptors influences the rate of platelet accumulation during thrombus formation.

Blood. 2004 Mar 15;103(6):2127-34

Effect of cilostazol on vasomotor reactivity in patients with vasospastic angina pectoris.

We examined the effects of cilostazol on impaired coronary arterial responses in patients with vasospastic angina (VSA). Thirty patients who were diagnosed with VSA based on an acetylcholine provocation test and 10 subjects with normal coronary arteries were enrolled. The patients were divided into the following 3 groups: no antiplatelet agent treatment group, aspirin treatment, or cilostazol treatment groups. Coronary flow reserve (CFR), coronary flow volume at maximum hyperemia, and epicardial coronary artery diameter after administration of N(G)-monomethyl-L-arginine (L-NMMA) were examined using a Doppler flow wire before and 6 months after the start of this study. CFR, coronary flow volume at maximum hyperemia, and diameter changes by L-NMMA were significantly increased in the cilostazol treatment group compared with the other 2 groups. In conclusion, cilostazol increased CFR and flow-dependent coronary dilation; these changes were attributable to nitric oxide. Cilostazol may improve coronary vascular endothelial dysfunction and coronary hemodynamics in patients with VSA.

Am J Cardiol. 2003 Jul 1;92(1):21-5

Effect of cilostazol on impaired vasodilatory response of the brachial artery to ischemia in smokers.

The vascular endothelial function of smokers is known to be impaired. This study investigated whether cilostazol could improve the vasodilatory response of the brachial artery to ischemia, an indicator of endothelial function, in ten male smokers. Endothelium-dependent vasodilatation and endothelium-independent vasodilatation of the brachial artery were measured in 11 male non-smokers and 20 male smokers with matching age and weight. The results showed that the vasodilatory response to reactive hyperemia was significantly smaller in the smokers (4.8 +/- 1.6%) when compared to that in the non-smokers (7.6 +/- 2.5%) (p = 0.0013). However, no significant difference in the vasodilatory response to isosorbide dinitrate was observed between the two groups. In addition, there were no significant differences in serum lipid, Lp (a), or blood homocysteine between the smokers and non-smokers. When 150 mg/day of cilostazol was administered for two weeks, the vasodilatory response to reactive hyperemia significantly improved (4.2 +/- 1.2% to 7.8 +/- 3.5%, p = 0.0032). The increased vasodilatory response to reactive hyperemia by cilostazol was reduced after cessation of the drug (4.5 +/- 1.5%). These findings suggest that cilostazol improves vascular endothelial dysfunction in smokers.

J Atheroscler Thromb. 2003;10(2):93-8.

Spontaneous recanalization of arterial occlusions: an unusual mechanism for symptomatic improvement.

OBJECTIVE: Patients with infrainguinal occlusive disease may experience spontaneous symptomatic improvement. This is generally thought to be from augmented collateral circulation. This study reports another mechanism. **METHODS:** Over a 20-year period, 4123 patients underwent lower extremity arteriography for limb ischemia. For a variety of reasons, 451 patients had repeat arteriography. **RESULTS:** Five patients were identified as having conclusive arteriographic evidence of spontaneous recanalization of occluded arterial segments without having undergone any surgical or thrombolytic interventions. Repeat contrast arteriography was performed on these patients for failing grafts (n = 2) or contralateral lower extremity ischemia (n = 3). Three other patients had magnetic resonance arteriographic or duplex arteriographic evidence of spontaneous arterial recanalization. Spontaneous recanalization occurred in iliofemoral (n = 2), superficial femoral (n = 2), popliteal (n = 3), and peroneal (n = 1) arterial segments. The average time interval of occlusion to recanalization was 21 weeks (2 weeks to 2 years). Two of the eight patients had failed revascularization procedures before spontaneous recanalization. All eight patients had restoration of pulses distal to the recanalized segments and significant symptomatic improvement as defined with the Society for Vascular Surgery/American Association for Vascular Surgery categories for limb ischemia. **CONCLUSION:**

Spontaneous recanalization of arterial segments can occur and must be considered when evaluating other proposed treatments of critical limb ischemia, including cilostazol, lytic agents, and angiogenic agents, such as vascular endothelial growth factor. Although its true incidence is unknown, this represents another mechanism for spontaneous symptomatic improvement without treatment in patients with severe limb ischemia.

J Vasc Surg. 2002 Dec;36(6):1161-6

Differential effects of cilostazol and pentoxifylline on vascular endothelial growth factor in patients with intermittent claudication.

Cilostazol is a new phosphodiesterase inhibitor with anti-platelet and vasodilatory properties. Cilostazol and pentoxifylline are the only two drugs that have been approved for the treatment of patients with intermittent claudication. However, the mechanisms by which exercise tolerance is improved remain unclear. Vascular endothelial growth factor (VEGF) is a potent endothelial mitogen that results in angiogenesis when overexpressed in human subjects. To assess the potential role of VEGF in the improvement in exercise tolerance, we investigated plasma levels of VEGF in 50 patients with intermittent claudication who were allocated randomly to groups receiving cilostazol (n=17), pentoxifylline (n=17) or placebo (n=16). Patients given either cilostazol or pentoxifylline showed a significant improvements in maximal walking distance compared with the placebo group (34 m and 33 m respectively, compared with 5 m; both P<0.05). Neither cilostazol nor pentoxifylline increased the ankle-brachial index after treatment. Circulating VEGF levels were increased (from 116 +/- 29 to 169 +/- 45 pg/ml; P=0.002), and the levels of VEGF were correlated significantly with exercise tolerance in a positive direction (r=0.88, P=0.004), in those patients treated with cilostazol that did not have diabetes mellitus. In contrast, VEGF levels remained stable after the administration of pentoxifylline. These findings suggest that VEGF may contribute to the cilostazol-related improvement in exercise tolerance in non-diabetic patients. However, pentoxifylline did not affect VEGF levels, although a similar improvement in maximal walking distance was achieved. Thus the mechanisms involved in the pentoxifylline-treated group were different from those in the cilostazol-treated group, and require further study.

Clin Sci (Lond). 2001 Sep;101(3):305-11.

Inhibition of neointimal formation after balloon injury by cilostazol, accompanied by improvement of endothelial dysfunction and induction of hepatocyte growth factor in rat diabetes model.

AIMS/HYPOTHESIS: Cilostazol, a well-known phosphodiesterase type 3 (PDE3) inhibitor for the treatment of peripheral arterial disease, has vasodilator properties

and an anti-proliferative action on the growth of vascular smooth muscle cells. In this study, we tested whether cilostazol inhibits neointimal formation and improves endothelial dysfunction after balloon injury in non-diabetic and diabetic rats. METHODS: Cilostazol or vehicle was administered to non-diabetic and streptozotocin-induced diabetic rats from 7 days before to 14 days after balloon injury of the carotid artery. We focused on the expression of hepatocyte growth factor to explore how cilostazol improved endothelial dysfunction. Also, we studied the effects of cilostazol on hepatocyte growth factor production in in vitro experiments. RESULTS: At 14 days after injury, the ratio of neointimal to medial area was decreased in rats treated with cilostazol in non-diabetic and diabetic animals. The impaired response to acetylcholine in balloon injured vessels was improved by cilostazol in non-diabetic and diabetic rats ($p < 0.05$). Vascular hepatocyte growth factor concentration was decreased in injured vessels of non-diabetic rats compared to uninjured vessels. Moreover, hepatocyte growth factor was further decreased in injured vessels of diabetic rats as compared to those of non-diabetic rats ($p < 0.05$). Of note, administration of cilostazol attenuated the decrease in hepatocyte growth factor concentration in injured vessels of both non-diabetic and diabetic rats ($p < 0.01$). Increase in vascular hepatocyte growth factor by cilostazol was confirmed by in vitro experiments showing that cilostazol increased hepatocyte growth factor concentration in cultured human vascular smooth muscle cells, accompanied by cAMP accumulation. CONCLUSION/INTERPRETATION: Our study shows that the increase in vascular hepatocyte growth factor by cilostazol could improve abnormal growth of vascular smooth muscle cells and endothelial dysfunction through rapid regeneration of endothelial cells.

Diabetologia. 2001 Aug;44(8):1034-42.

[Hypertension and endothelial dysfunction in apolipoprotein E knockout mice.](#)

Mice lacking ApoE (ApoE^{-/-}) develop initially hypercholesterolemia and lastly atherosclerosis. This study examined hemodynamics and endothelial function in 6-week-old ApoE^{-/-} mice with hypercholesterolemia only, 7.5-months-old ApoE^{-/-} mice with both hypercholesterolemia and atherosclerosis, and age matched controls. One day after implantation of catheters into the carotid artery, arterial pressure was measured in conscious, unrestrained mice. Compared with the respective controls, there was a significant increase in arterial pressure and the ratio of left ventricular weight to body weight in 7.5-month-old ApoE^{-/-} mice but not in 6-week-old ApoE^{-/-} mice. Histopathological analysis demonstrated significant renal artery disease in the form of extensive atheromatous plaques only in 7.5-month-old ApoE^{-/-} mice, whereas no atherosclerotic lesions were found in 6-week-old ApoE^{-/-} mice. For evaluation of endothelial function, a laser Doppler perfusion imager with a computer-controlled optical scanner was used to measure

cutaneous blood perfusion on the dorsal side of one hind paw before and after topical application of mustard oil, which is known to induce nitric oxide-mediated vasodilation. The mustard oil treatment elicited a substantial increase in blood perfusion ($P < 0.01$), which was similar between 6-week-old ApoE^{-/-} mice and controls but significantly blunted in 7.5-month-old ApoE^{-/-} mice versus control mice, suggesting nitric oxide-mediated vasodilation is diminished in 7.5-month-old ApoE^{-/-} mice but not in 6-week-old ApoE^{-/-} mice. In contrast, the increase in blood perfusion induced by topical administration of cilostazol, which induces vasodilation via cyclic adenosine monophosphate, was not different between 7.5-month-old ApoE^{-/-} mice and controls. Thus hypertension and endothelial dysfunction observed in 7.5-month-old ApoE^{-/-} mice may be due mainly to atherosclerosis.

Arterioscler Thromb Vasc Biol. 1999;19(11):2762.

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