

Effects of cilostazol on platelet activation in coronary stenting patients who already treated with aspirin and clopidogrel.

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BACKGROUND: A recent study has shown that triple anti-platelet therapy (cilostazol+clopidogrel+aspirin) resulted in a significantly lower restenosis rate after coronary stenting than did conventional therapy (clopidogrel+aspirin). However, the anti-platelet effects of cilostazol, when combined with clopidogrel and aspirin, have not been evaluated. **METHODS:** Low dose cilostazol (50 mg/BID) was given to 47 patients who had already been taking clopidogrel (75 mg/day) and aspirin (100 mg/day) for more than 1 month subsequent to coronary stenting due to AMI and unstable angina. Markers of platelet activation, P-selectin and activated GPIIb/IIIa on platelets, were measured at baseline and 2 weeks after cilostazol treatment. We empirically divided patients into tertiles (low, n =16; moderate, n = 14; high group, n = 17), according to the baseline P-selectin expression. We then performed a comparative assessment of the anti-platelet effects of cilostazol at baseline and after 2 weeks of cilostazol administration. **RESULTS:** P-selectin was significantly decreased after 2 weeks of cilostazol treatment in total patients (n = 47, 3.2 +/- 2.4% to 2.0 +/- 1.9%, p = 0.03). This inhibition of P-selectin expression was mainly achieved in the moderate and high P-selectin groups (low group; 1.4 +/- 0.5 to 1.9 +/- 1.3%, p > 0.05, moderate group; 2.5 +/- 0.3 to 1.3 +/- 0.3%, p < 0.05, high group; 5.4 +/- 2.7 to 2.7 +/- 2.8%, p < 0.05). Activated GPIIb/IIIa was not significantly changed (13.5% to 17.6%, p > 0.05). Underlying disease, cardiovascular risk factors, concomitant medication including statin, and hsCRP were not related to the degree of P-selectin expression. **CONCLUSION:** Our data demonstrated that cilostazol treatment in addition to conventional anti-platelet therapy provides more effective suppression of platelet P-selectin expression in patients with relatively high platelet activity.

Management of peripheral arterial disease.

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Peripheral arterial disease (PAD) may be asymptomatic, may be associated with intermittent claudication, or may be associated with critical limb ischemia. Coronary artery disease (CAD) and other atherosclerotic vascular disorders may coexist with PAD. Persons with PAD are at increased risk for all-cause mortality, cardiovascular mortality, and mortality from CAD. Modifiable risk factors such as cessation of cigarette smoking and control of dyslipidemia, hypertension, and diabetes should be treated. Statins reduce the incidence of intermittent claudication and improve exercise duration until the onset of intermittent claudication in persons with PAD and hypercholesterolemia. Antiplatelet drugs such as aspirin or clopidogrel, especially clopidogrel, and angiotensin-converting enzyme inhibitors should be given to all persons with PAD. beta-Blockers should be given if CAD is present. Exercise rehabilitation programs and cilostazol improve exercise time until intermittent claudication. Indications for lower-extremity angioplasty, preferably with stenting, or bypass surgery are 1) incapacitating claudication in persons interfering with work or lifestyle; 2) limb salvage in persons with limb-threatening ischemia as manifested by rest pain, nonhealing ulcers, and/or infection or gangrene; and 3) vasculogenic impotence. However, amputation should be performed if tissue loss has progressed beyond the point of salvage, if surgery is too risky, if life expectancy is very low, or if functional limitations diminish the benefit of limb salvage.

Cilostazol Inhibits Vascular Smooth Muscle Cell Growth by Downregulation of the Transcription Factor E2F.

Hypertension. 2005 Feb 21

Neointimal formation, the leading cause of restenosis, is caused by proliferation of vascular smooth muscle cells (VSMCs). Patients with diabetes mellitus have higher restenosis rates after coronary angioplasty than nondiabetic patients. Cilostazol, a selective type 3 phosphodiesterase inhibitor, is currently used to treat patients with diabetic vascular complications. Cilostazol is a potent antiplatelet agent that inhibits VSMC

proliferation. In the present study, we examine whether the antiproliferative effect of cilostazol on VSMCs is mediated by inhibition of an important cell cycle transcription factor, E2F. Cilostazol inhibited the proliferation of human VSMCs in response to high glucose in vitro and virtually abolished neointimal formation in rats subjected to carotid artery injury in vivo. Moreover, the compound suppressed high-glucose-induced E2F-DNA binding activity, and the expression of E2F1, E2F2, cyclin A, and PCNA proteins. These data suggest that the beneficial effects of cilostazol on high-glucose-stimulated proliferation of VSMCs are mediated by the downregulation of E2F activity and expression of its downstream target genes, including E2F1, E2F2, cyclin A, and PCNA.

Cilostazol Reduces Atherosclerosis by Inhibition of Superoxide and TNF- α Formation in Low-density Lipoprotein Receptor-null Mice fed High Cholesterol.

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This study shows that cilostazol suppresses the atherosclerotic lesion formation in the low density lipoprotein receptor (Ldlr)-null mice. Ldlr-null mice fed high cholesterol diet showed multiple plaque lesions in the proximal ascending aorta including aortic sinus, accompanied by increased macrophage accumulation with increased expression of vascular cell adhesion molecule-1 (VCAM-1), monocyte chemoattractant protein-1 (MCP-1). Supplementation of cilostazol (0.2% w/w) in diet significantly decreased the plaque lesions with reduced macrophage accumulation and suppression of VCAM-1 and MCP-1 in situ. Increased superoxide and TNF- α production were significantly lowered by cilostazol in situ as well as in cultured HUVECs. TNF- α -induced increased inhibitory κ B (I κ B) degradation in the cytoplasm and nuclear factor- κ B (NF- κ B) p65 activation in the nuclei of HUVECs were reversed by cilostazol (1 ~100 microM) as well as by BAY 11-7085 (10 microM), suggesting that cilostazol strongly inhibits NF- κ B activation and p65 translocation into the nuclei. Further, in gel shift and DNA-binding assay, cilostazol inhibited NF- κ B/DNA complex and nuclear DNA-binding activity of the NF- κ B in the nuclear extracts of the RAW 264.7 cells. Taken together, it is suggested that the anti-atherogenic effect of cilostazol in cholesterol-fed Ldlr-null mice

is ascribed to its property to suppress superoxide and TNF- α formation, and thereby reducing NF- κ B activation/transcription, VCAM-1/MCP-1 expressions, and monocyte recruitments.

The effect of a late evening snack in patients with liver cirrhosis.

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OBJECTIVES:: As an intervention for energy malnutrition, frequent meals or a late evening snack (LES) has been recently recommended. On the other hand, it has been reported that glucose intolerance is found in approximately 70% of patients with liver cirrhosis. Thus, we investigated which would be better for the improvement of energy malnutrition and glucose intolerance, treatment with LES alone or LES plus divided meals.

METHODS:: One group of oral supplementation with one pack of a branched-chain amino acid (BCAA)-enriched nutrient, Aminoleban EN (210kcal), at 10 p.m. LES and the other group with two packs of Aminoleban EN (one pack at 10 p.m. as LES and another pack during the day, i.e. at sometime from 10 a.m. to 3 p.m.) were examined to determine the influence of LES on the blood glucose level, biochemical parameters, and energy metabolism. Twenty-six patients participated in this study. The administration period was 7 days. Metabolic measurements were performed using an indirect calorimeter.

RESULTS:: The fat oxidation rate was significantly decreased and the carbohydrate oxidation rate significantly increased in both groups. As a result, respiratory quotient (RQ) was significantly improved. In many cases, the increase of the glucose level after meals seemed to be reduced after LES administration for 1 week. LES could improve energy malnutrition, and correct amino acid imbalance. There was also a significant correlation between non-protein respiratory quotient (npRQ) and the creatinine height index.

CONCLUSION:: LES alone improved the energy malnutrition state and glucose intolerance equivalent to LES plus divided meals. Thus, LES may improve glucose intolerance in patients with liver cirrhosis.

<http://www.thai-otsuka.co.th/pxnews/index.html> Opinions and suggestions are welcomed Dr. Shwe Win, shwewin@thai-otsuka.co.th