

TOP Journal Club

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A randomized crossover comparative study of aspirin, cilostazol and clopidogrel in normal controls: analysis with quantitative bleeding time and platelet aggregation test.

Reference: Clin Neurosci. 2004 ;11(6):600-2.

The effects of three antiplatelet drugs, aspirin, clopidogrel and cilostazol, were examined and compared using a quantitative bleeding time (QBT) test apparatus. In 12 healthy adult male subjects, a QBT test and platelet aggregation test were performed before and after medication. Cilostazol was found to be as effective as aspirin and clopidogrel in inhibiting platelet aggregation. Following the oral administration of aspirin and clopidogrel for 7 days, the bleeding time was significantly prolonged. In contrast, none of these QBT parameters were altered by the cilostazol treatment. This suggests that cilostazol has potent efficacy in inhibiting platelet aggregation without prolonging the bleeding time and changing the bleeding pattern.

Drug treatment of intermittent claudication.

Reference: Drugs. 2004;64(15):1657-70

The US FDA has approved two drugs for the management of intermittent claudication: pentoxifylline and cilostazol. The mechanism of action that provides symptom relief with pentoxifylline is poorly understood but is thought to involve red blood cell deformability as well as a reduction in fibrinogen concentration, platelet adhesiveness and whole blood viscosity. The recommended dose of pentoxifylline is 400mg three times daily with meals. Cilostazol is a potent, reversible, phosphodiesterase III inhibitor. The inhibition of phosphodiesterase allows for the increased availability of cyclic adenosine monophosphate (cAMP). cAMP mediates many agonist-induced platelet inhibitory, vasodilatory and vascular antiproliferative

responses. Cilostazol, at a dose of 100mg twice daily, is recommended to be taken 30 minutes before or 2 hours after breakfast and dinner. In addition to pentoxifylline and cilostazol, clinical trials indicate many other drugs may relieve the symptoms of intermittent claudication. Ginkgo biloba, available as an over-the-counter extract, provides symptom relief comparable to pentoxifylline. Two European agents, naftidrofuryl and buflomedil, also have efficacy that is reported to be similar to pentoxifylline. Policosanol is a mixture of fatty alcohols derived from honeybee wax which, according to very limited data, reduces symptoms of claudication. Amino acids, certain peptides and prostaglandins may have a therapeutic role. Finally, novel approaches including angiogenesis mediated by growth factors, are currently under investigation

Cilostazol and Dipyridamole Synergistically Inhibit Human Platelet Aggregation.

Reference: J Cardiovasc Pharmacol. 2004 Aug;44(2):266-273

It has been previously shown that cilostazol (Pletal), a drug for relief of symptoms of intermittent claudication, potently inhibits cyclic nucleotide phosphodiesterase type 3 (PDE3) and moderately inhibits adenosine uptake. It elevates extracellular adenosine concentration, by inhibiting adenosine uptake, and combines with PDE3 inhibition to augment inhibition of platelet aggregation and vasodilation while attenuating positive chronotropic and inotropic effects on the heart. In the present study, we tested the hypothesis that cilostazol combined with a more potent adenosine uptake inhibitor, dipyridamole, synergistically inhibited platelet aggregation in human blood. In the presence of exogenous adenosine (1 microM), the combination of cilostazol and dipyridamole synergistically increased intra-platelet cAMP. Furthermore, cilostazol inhibited platelet aggregation in a washed platelet assay concentration-dependently with IC₅₀s of 0.17 +/- 0.04 microM (P < 0.05 versus plus adenosine alone of 0.38 +/- 0.05 microM), 0.11 +/- 0.06

microM ($P < 0.05$), and 0.01 ± 0.01 microM ($P < 0.005$) when combined with 1, 3, or 10 microM dipyridamole, respectively ($n = 5$). In whole blood, cilostazol (0.3 to 3 microM) and dipyridamole (1 or 3 microM) synergistically inhibited collagen- and ADP-induced platelet aggregation in vitro. Furthermore, the synergism was confirmed in an open-label, sequential study in healthy human subjects using ex vivo whole-blood collagen-induced platelet aggregation. Four hours after oral co-administration of cilostazol (100 mg) and dipyridamole (200 mg), platelet aggregation was inhibited by $45 \pm 17\%$, while no significant inhibition was observed from subjects treated with either drug alone. The combination may provide a potential treatment of arterial thrombotic disorders.

Comparison of Cilostazol and Ticlopidine for One-Month Effectiveness and Safety after Elective Coronary Stenting.

Reference: *Cardiovasc Drugs Ther.* 2004 May;18(3):211-217

Purpose: To compare the oral antiplatelets, phosphodiesterase III inhibitor cilostazol and the thienopyridine ticlopidine, for one-month effectiveness and safety as an adjunctive therapy after coronary stenting. **Methods:** Published studies retrieved through Medline and other databases from 1966-2002. Meta-analyses evaluated effectiveness and adverse side effects for one-month administrations of aspirin plus cilostazol or aspirin plus ticlopidine therapy after coronary stenting. Major adverse cardiac events (MACE), stent-associated thrombosis or adverse side effects after coronary stenting were compared between the two study arms and expressed with the odds ratios (OR) specific for the individual studies and meta-analytic summary for OR. **Results:** Five clinical studies met the inclusion criteria, and 4 of these studies underwent meta-analysis. With regard to the comparison of the OR summary for MACE and stent-associated thrombosis for the clinical outcome, there were no statistical significant differences between aspirin plus cilostazol and aspirin plus ticlopidine. While, the incidence of adverse side effects tended to

be lower, they were not statistically significant in patients with aspirin plus cilostazol. **Conclusions:** Our meta-analysis results indicated that there were no differences between cilostazol (plus aspirin) and ticlopidine (plus aspirin) with regard to effectiveness and safety for a one-month period when used as an adjunctive therapy after coronary stenting.

Effects of antiplatelet agents on subacute thrombosis and restenosis after successful coronary stenting: a randomized comparison of ticlopidine and cilostazol.

Reference: *Circ J.* 2004 Jul;68(7):610-4.

BACKGROUND: A prospective randomized study compared the preventive effects of ticlopidine plus aspirin therapy versus cilostazol plus aspirin therapy on subacute thrombosis (SAT) and restenosis after coronary stenting. **METHODS AND RESULTS:** After successful stenting of 327 coronary lesions in 282 consecutive patients, the patients were randomized to receive ticlopidine (200 mg/day) or cilostazol (200 mg/day). Aspirin (81 mg/day) was administered concomitantly in both groups. SAT occurred in 1 patient in the ticlopidine group (0.7%) and in 8 patients in the cilostazol group (5.6%, $p=0.037$). Based on follow-up angiography, restenosis occurred in 30 patients (23.3%) in the ticlopidine group and 35 patients (26.9%) in the cilostazol group (NS). The late loss was significantly smaller in the cilostazol group than the ticlopidine group (1.08 ± 0.95 mm vs 0.78 ± 0.93 mm, respectively, $p=0.037$). No significant differences between the 2 groups were observed with respect to the rates of total death, non-fatal cardiovascular events, or bleeding complications. **CONCLUSION:** The ticlopidine group showed significantly less SAT after stenting compared with the cilostazol group. After 6 months of treatment, the inhibition of neointimal proliferation was greater in the cilostazol group than in the ticlopidine group, but the prevention of restenosis was not confirmed

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