

TOP Journal Club

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Cilostazol: a review of its use in intermittent claudication.

Reference: Am J Cardiovasc Drugs. 2003; 3(2): 117.

Cilostazol (Pletal((R))) is a selective inhibitor of phosphodiesterase-III with antiplatelet, antithrombotic and vasodilating properties. It also exhibits antiproliferative effects on smooth muscle cells and has beneficial effects on high density lipoprotein-cholesterol and triglyceride levels. Randomized, double-blind, placebo-controlled 12- to 24-week trials in >2000 patients with moderate to severe intermittent claudication demonstrated that cilostazol generally significantly increased walking distances and improved quality of life compared with placebo. Additionally, a large comparative 24-week trial showed that cilostazol 100mg twice daily was significantly more effective than pentoxifylline 400mg three times daily (pentoxifylline was not significantly different from placebo). Cilostazol was generally well tolerated. Adverse events reported significantly more often with cilostazol than with placebo included headache, diarrhea, abnormal stools, infection, rhinitis and peripheral edema and in comparison with pentoxifylline were headache, diarrhea, abnormal stools and palpitations. Adverse events were generally mild to moderate in intensity, transient or resolved after symptomatic treatment and rarely required treatment withdrawal. Significant drug interactions are observed when cilostazol is coadministered with other agents that inhibit cytochrome P450 (CYP) 3A4 (e.g. erythromycin or diltiazem) or CYP2C19 (e.g. omeprazole). As a result, in Europe cilostazol is contraindicated in patients receiving CYP3A4 or CYP2C19 inhibitors and in the US it is recommended that dosage reduction for cilostazol be considered during coadministration of cilostazol and CYP3A4 or CYP2C19 inhibitors. Conversely, cilostazol itself does not appear to inhibit CYP3A4. Coadministration of cilostazol with aspirin or warfarin did not result in any clinically significant changes to coagulation parameters, bleeding time or platelet aggregation. **CONCLUSION:** In six of eight well designed clinical trials, cilostazol was significantly more effective than placebo in increasing walking distances and improving the

quality of life of patients with moderate to severe intermittent claudication. In addition, limited comparative data have shown that cilostazol has superior efficacy compared with pentoxifylline. Cilostazol is also generally well tolerated. Additional comparative trials are required to confirm these results, to determine the place of cilostazol in relation to other agents or exercise therapy and risk factor reduction alone, and to establish the effects of long-term treatment with cilostazol in patients with intermittent claudication. Cilostazol is contraindicated in several subpopulations of patients, particularly those with congestive heart failure and severe hepatic or renal impairment. Nonetheless, current data support the choice of cilostazol as a promising therapy amongst the limited options available for patients with intermittent claudication.

Effects of antiplatelet agents on pulmonary haemodynamic response to fMLP in endotoxin primed rats.

Reference: Thorax. 2004 Jan; 59(1): 39-44.

BACKGROUND: The interaction between neutrophils and platelets may be important in the modulation of pulmonary haemodynamics under systemic inflammatory conditions. A study was undertaken to examine whether antiplatelet agents inhibit platelet-neutrophil adherence and ameliorate the pulmonary haemodynamic response to fMLP by inhibiting thromboxane release in endotoxin primed lungs. fMLP stimulates neutrophils but not platelets; however, thromboxane synthesis in neutrophils is very low. **METHODS:** Rats were pretreated with either cilostazol (300 mg/kg) or aspirin (50 mg/kg) before endotoxin priming (5 mg/kg). Platelets in the lung were identified by fluorescent immunohistochemistry. Platelet-neutrophil adherence was analysed by flow cytometry of the lung vascular flush. The effect of fMLP (10(-6) M) on thromboxane release, lung weight (an indicator of pulmonary vasoconstriction), and lung filtration coefficient was determined in an isolated lung system perfused at a constant pressure difference. **RESULTS:** Endotoxin induced platelet accumulation and platelet-neutrophil adherence in the lung capillary were completely inhibited by cilostazol and aspirin while neutrophil recruitment was not affected. The fMLP challenge caused a

significant increase in thromboxane B2 levels in endotoxin primed lungs. The fMLP induced decrease in lung weight was enhanced by endotoxin priming (from -4.9 to -63.9 mg, 95% CI of mean difference -99.5 to -10.5 mg, $p < 0.05$). The fMLP induced increase in the lung filtration coefficient was also enhanced by endotoxin priming (from 0.63 to 2.40 mg/min/cm H₂O/g, 95% CI of mean difference 1.17 to 2.37 mg/min/cm H₂O/g, $p < 0.05$). Treatment with cilostazol and aspirin completely inhibited the enhanced pulmonary haemodynamic response to fMLP. CONCLUSION: The neutrophil-platelet interaction is of critical importance in the modulation of pulmonary haemodynamics via thromboxane.

A method for evaluating drug effects on intermittent claudication using a treadmill in rats with unilateral hindlimb artery occlusion.

Reference: J Pharmacol Toxicol Methods. 2004 Jan-Feb; 49(1): 25-9.

INTRODUCTION: We have developed an in vivo experimental model for evaluating peripheral arterial insufficiency and predicting the efficacy of drugs on intermittent claudication (IC). We found that rats that had been running normally on a treadmill developed a gait disturbance when a hindlimb artery was unilaterally occluded. We hypothesized that the distance run before gait disturbance developed (DGD) in rats with occlusion of a hindlimb artery might be an appropriate index of the severity of peripheral insufficiency, and that the model might serve as a test bed for evaluating drug efficacy. To prove this hypothesis, we examined whether DGD was determined by severity of hindlimb ischemia. Furthermore, we also examined whether cilostazol, which has been proved to have ameliorative effects in patients with IC, increased DGD. METHODS: To vary the severity of ischemia, either the superficial femoral artery, the distal portion of the iliac artery, or the proximal portion of iliac artery was unilaterally occluded. After a recovery period, these rats were subjected to a treadmill test (15 m/min and 15% incline) to determine DGD and examine the effect of cilostazol on DGD. RESULTS: DGD was the longest and shortest in rats with superficial

femoral artery and proximal portion of iliac artery occlusion, respectively. Intermediate DGD was observed in rats with distal portion of iliac artery occlusion. These data suggest that DGD is correlated with the severity of hindlimb ischemia. Two weeks or longer administration of cilostazol 30 and 100 mg/kg twice a day evoked a significant increase in DGD. DISCUSSION: Peripheral arterial insufficiency and its modulation by drugs can be evaluated in rats with unilateral hindlimb artery occlusion, on a treadmill, by measuring DGD.

Effects of liver failure on the enzymes in the branched-chain amino acid catabolic pathway.

Reference: Biochem Biophys Res Commun. 2004 Jan 9; 313(2): 381-5.

Branched-chain alpha-keto acid dehydrogenase (BCKDH) complex catalyzes the committed step of the catabolism of branched-chain amino acids (BCAA). The liver cirrhosis chemically induced in rats raised the activity of hepatic BCKDH complex and decreased plasma BCAA and branched-chain alpha-keto acid concentrations, suggesting that the BCAA requirement is increased in liver cirrhosis. Since the effects of liver cirrhosis on the BCKDH complex in human liver are different from those in rat liver, further studies are needed to clarify the differences between rats and humans. In the valine catabolic pathway, crotonase and beta-hydroxyisobutyryl-CoA hydrolase are very important to regulate the toxic concentration of mitochondrial methacrylyl-CoA, which occurs in the middle part of valine pathway and highly reacts with free thiol compounds. Both enzyme activities in human and rat livers are very high compared to that of BCKDH complex. It has been found that both enzyme activities in human livers were significantly reduced by liver cirrhosis and hepatocellular carcinoma, suggesting a decrease in the capability to dispose methacrylyl-CoA. The findings described here suggest that alterations in hepatic enzyme activities in the BCAA catabolism are associated with liver failure.

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