

TOP Journal Club

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Reduction of remnant lipoprotein cholesterol concentrations by cilostazol in patients with intermittent claudication.

Reference: Atherosclerosis. 2003;171(2):337

BACKGROUND: Elevated triglyceride-rich lipoproteins and reduced high-density lipoproteins (HDL) are associated with the development of intermittent claudication (IC), a life-limiting symptom of peripheral arterial disease. Cilostazol, a potent platelet inhibitor and vasodilator, lowers triglycerides and increases HDL concentrations in addition to increasing walking distance in patients with intermittent claudication. However, the association of remnant lipoproteins (a more atherogenic subset of triglyceride-rich lipoproteins) and peripheral arterial disease and the effects of cilostazol on remnant lipoproteins have not been studied. **METHODS AND RESULTS:** We quantified plasma remnant lipoprotein concentrations using the remnant lipoprotein-cholesterol assay (RLP-C). Patients with intermittent claudication (n=415) had significantly higher remnant lipoprotein concentrations compared to reference subjects (n=874; 0.31 ± 0.32 versus 0.24 ± 0.17 mmol/l, $P < 0.001$) in addition to elevated total triglyceride (2.67 ± 1.92 versus 1.92 ± 1.24 mmol/l, $P < 0.001$) and reduced high-density lipoprotein (HDL) cholesterol concentrations (1.06 ± 0.31 versus 1.22 ± 0.36 mmol/l, $P < 0.001$). Cilostazol treatment (100mg, b.i.d.) in patients with intermittent claudication (n=56) for 6 months resulted in 20% reduction of remnant lipoprotein-cholesterol (from 0.27 ± 0.21 to 0.22 ± 0.09 mmol/l, $P < 0.05$) versus no significant change (from 0.26 ± 0.17 to 0.27 ± 0.12 mmol/l) in the placebo group (n=67). Cilostazol also reduced triglyceride concentrations significantly (from 2.32 ± 1.46 to 1.79 ± 0.72 mmol/l, $P < 0.01$, in the cilostazol group versus 2.38 ± 1.39 to 2.25 ± 1.19 mmol/l

in the placebo group) and increased HDL cholesterol concentrations (from 1.06 ± 0.23 to 1.24 ± 0.34 mmol/l, $P < 0.001$) in the cilostazol group versus no significant change (1.06 ± 0.34 to 1.09 ± 0.36 mmol/l) in the placebo group. Pentoxifylline (400mg, t.i.d.) did not have any significant effects on lipid variables (n=66). **CONCLUSIONS:** Remnant lipoprotein concentrations are significantly elevated in patients with intermittent claudication and can be reduced by cilostazol. Reduction of remnant lipoproteins may provide a long-term benefit to the patients with symptomatic peripheral arterial disease.

Cilostazol reduces brain lesion induced by focal cerebral ischemia in rats--an MRI study.

Reference: Brain Res. 2003;19:994(1):91-8.

To investigate the effects of cilostazol on the hemispheric ischemic lesion, we monitored the apparent diffusion coefficient (ADC) and T2 images by MRI techniques in comparison with histology at the terminal of and after 24-h reperfusion following 2-h occlusion of middle cerebral artery (MCA). The ADC values of tissue water and T2-weighted images were quantified by high field magnetic resonance. No significant difference was observed by ADC image among vehicle and cilostazol treatment groups when measured during MCA occlusion. Oral treatment with cilostazol 30 mg/kg two times at 5 min and 4 h significantly suppressed the hemispheric lesion area and volumes when detected by ADC, T2 images and histology, but 3 and 10 mg/kg cilostazol were without effect. Cilostazol (30 mg/kg) significantly reduced the increased cerebral water content at the ischemic hemisphere compared with vehicle group. In line with these results, the neurological deteriorations were much improved in the cilostazol-treated group. Taken together, it is concluded that post-treatment with cilostazol exerts a potent protective effect against cerebral infarct size by reducing the cytotoxic edema.

Preoperative administration of rebamipide significantly lowers body temperature and circulating interleukin-6 in gastric cancer patients after gastrectomy.

Reference: Dig Surg. 2003;20(6):500-5

BACKGROUND/AIMS: It has recently been reported that rebamipide (OPC-12759) inhibits inflammatory cytokines and activation of neutrophils. The aim of the present study was to investigate the effects of preoperative administration of rebamipide on parameters of systemic inflammatory response syndrome (SIRS) and serum levels of inflammatory cytokines in gastric cancer patients after gastrectomy. **PATIENTS AND METHODS:** We measured the parameters of SIRS, circulating cytokines and acute phase reactants in patients after (i). distal gastrectomy with D2 lymph node dissection (group 1, n = 10); (ii). distal gastrectomy with D2 lymph node dissection following administration of rebamipide (group 2, n = 10), and (iii). laparoscopy-assisted distal gastrectomy (LADG) with D1 lymph node dissection (group 3, n = 10). Group 2 was administered 100 mg of rebamipide 3 times/day after meals for 7 days before surgery. **RESULTS:** Among the parameters of SIRS, a difference was observed in body temperature on day 3. The mean body temperature of group 2 was significantly lower than group 1 ($p = 0.006$), and was similar to group 3. In proinflammatory cytokines, a significant difference was observed in the serum levels of interleukin (IL)-6. On day 1 the IL-6 levels of group 2 were significantly lower than those of group 1 ($p < 0.001$). The changes in the IL-6 level of group 2 were similar to group 3, except in the very early postoperative phase. However, other proinflammatory cytokines, such as IL-8 and IL-10, were not detected, and there was no difference in C-reactive protein between the 3 groups. **CONCLUSION:** Preoperative administration of rebamipide significantly decreased postoperative body temperatures and circulating IL-6 in gastric cancer patients

after gastrectomy to levels similar to those of patients with LADG.

Influence of anti-ulcer drugs used in Japan on the result of (13)C-urea breath test for the diagnosis of Helicobacter pylori infection.

Reference: J Gastroenterol. 2003;38(10):937.

BACKGROUND: The (13)C-urea breath test (UBT) is a simple breath test for the diagnosis of Helicobacter pylori infection, but several factors have been reported to affect the results of this test. In this study, the effects of the antiulcer drugs used in Japan on the results of UBT were determined. **METHODS:** The subjects of the study were 64 adult volunteers who tested positive for H. pylori infection by the serum antibody method. Eight classes of anti-ulcer drugs used in Japan were administered at their usual doses to these subjects: lansoprazole, a proton pump inhibitor (PPI); nizatidine, an H(2)-receptor antagonist (H(2)RA); and polaprezinc, ecabet sodium, rebamipide, teprenone, cetraxate hydrochloride, and sucralfate, all mucoprotective agents. The study drugs were randomized for administration to the subjects, and each of the drugs was administered for 14 consecutive days. The UBT was performed on days 0, 14, and 21. **RESULTS:** The mean Delta(13)C per thousand in the lansoprazole group was significantly decreased on day 14, to below 10 per thousand, in 4 of 16 subjects, and in 1 of the 4 subjects, the test result was negative, with the Delta(13)C per thousand falling to 1.7 per thousand. The value returned to baseline 1 week after the discontinuation of lansoprazole. The other drugs administered had no significant effect on the result of the UBT, except that the mean Delta(13)C per thousand showed a tendency to decrease after the administration of ecabet sodium and rebamipide. **CONCLUSIONS:** Administration of a PPI may produce a false-negative UBT result, while other anti-ulcer drugs, for the most part, have little effect on the result of the UBT when used alone. The (13)C-urea breath test (UBT) is a

simple test for the diagnosis of Helicobacter pylori infection, but several factors have been reported to affect the results of this test. In this study, the effects of the anti-ulcer drugs used in Japan on the results of the UBT were determined.

Changes in ankle brachial index in symptomatic and asymptomatic subjects in the general population.

Reference: J Vasc Surg. 2003 Dec;38(6):1323
OBJECTIVE: To determine changes over time in the ankle brachial index (ABI) among subjects with and without intermittent claudication in the general population. DESIGN OF STUDY: Population cohort study. SETTING: General population in Edinburgh, Scotland. SUBJECTS: A total of 1592 men and women aged 55 to 74 years selected at random from age-sex registers of 11 general practices and followed up over 12 years. Main outcome measures Changes in ABI for each leg recorded at baseline in 1988 and at subsequent 5-year and 12-year clinical examinations. RESULTS: Overall, 695 subjects (348 men and 347 women) had valid ABI measurements on both legs at all three examinations. At baseline, the ABI was on average .03 higher in the right leg than the left ($P < \text{or} = .001$). Men had a mean ABI that was .07 higher than women ($P < \text{or} = .001$). Mean ABI in the worse leg showed little change over 12 years in both men and women. However, in the whole population, the ABI in the better leg showed a significant drop, 1.15 to 1.08 ($P < \text{or} = .001$). A total of 179 cases of intermittent claudication were identified during the 12-year follow-up. At baseline, ABI in the worse leg of the claudicants was significantly lower than in healthy subjects (.99 vs 1.08; $P < \text{or} = .01$). In claudicants, mean ABI in the worse leg fell by .04 over 5 years ($P < \text{or} = .05$) and in the better leg showed a highly significant drop of .09 ($P < \text{or} = .001$) to levels similar to those of the worse leg. CONCLUSIONS: The mean ABI in the worse leg of study subjects showed little progression over 12 years. Individuals with intermittent

claudication experienced a greater decline in both legs compared with those without claudication. Deterioration occurred more rapidly in the limb with a higher ABI at baseline, which possibly indicates a systemic tendency to atherosclerosis.

Thrombogenesis and endothelial damage/dysfunction in peripheral artery disease. Relationship to ethnicity and disease severity.

Reference: Thromb Res. 2003;111(4-5):221

Peripheral artery disease (PAD) and intermittent claudication are common in men aged over 55 years. Once the diagnosis has been made, very few patients suffer from a deterioration of the disease. Those that do deteriorate tend to do so due to thrombosis of an affected artery. It is apparent that the disruption in the vessel wall accounts for some of the cause of the thrombosis but blood constituents also play a role. We hypothesized that levels of soluble P-selectin (sP-sel, a marker of platelet activation), von Willebrand factor (vWf, an index of endothelial damage/dysfunction), tissue factor (TF, a coagulation protein involved in the 'extrinsic' coagulation pathway) and fibrinogen would be abnormally elevated in relation to disease severity and correlated with each other, and related to ethnicity, in a multiethnic population of patients with PAD. To test this hypothesis, we studied 234 patients (80% white, 7% Indo-Asian, 13% Afro-Caribbean) with confirmed PAD [ankle brachial pressure index (ABPI) ≤ 0.8] and 50 healthy controls. All of the indices studied were increased in patients over controls ($p < 0.05$). None of the indices of the hypercoagulable state were significantly different between the three ethnic groups studied. Patients with ischaemic rest pain were shown to have higher levels of plasma fibrinogen ($p < 0.001$) although none of the other prothrombotic markers were increased in this group. Furthermore, fibrinogen was higher in cases whose ABPI was below the median (< 0.52) when compared to those less severely

affected, with an inverse correlation between fibrinogen and ABPI (Spearman, $r=-0.178$, $p=0.009$). In conclusion, we found a prothrombotic state in patients with PAD with increased levels of markers of endothelial damage/dysfunction, platelet activation and thrombosis, which may contribute to the pathogenesis of this condition. However, disease severity was only related to plasma fibrinogen levels.

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