

# TOP Journal Club

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## Evaluation of anti-platelet aggregatory effects of aspirin, cilostazol and ramatroban on platelet-rich plasma and whole blood.

Reference: Blood Coagul Fibrinolysis. 2004 Mar;15(2):157-67

To compare property in anti-platelet effects of aspirin (a cyclooxygenase inhibitor), cilostazol (a phosphodiesterase III inhibitor) and ramatroban (a specific thromboxane A2 receptor antagonist), we measured human platelet-rich plasma (PRP) aggregation induced by adenosine diphosphate (ADP), collagen and arachidonic acid, and whole blood (WB) aggregation induced by ADP. The release of P-selectin, transforming growth factor-beta 1, and the formation of thromboxane A2 in response to agonists were also investigated. Inhibitory effects of 100 micromol/l aspirin, 10 micromol/l cilostazol and 1 micromol/l ramatroban on 5 micromol/l ADP-induced PRP aggregation were similar. However, aspirin strongly inhibited thromboxane A2 formation in response to 5 micromol/l ADP compared with other drugs. Inhibitory effects of 10 micromol/l cilostazol on PRP aggregation and the release of molecules were quite similar in responsiveness induced by the three agonists. Aspirin and cilostazol inhibited platelet aggregation in a concentration-dependent, non-linear fashion, while ramatroban inhibited linearly with increasing concentration. Anti-platelet effects of drugs having different pharmacological mechanisms were demonstrated clearly by measuring PRP aggregation induced by the three agonists, and by measuring WB aggregation that most probably reflects not only platelet-platelet interactions, but also platelet-leukocyte interactions, as well as the release of intraplatelet molecules.

## Peripheral arterial disease. A systemic disease extending beyond the affected extremity.

Reference: Geriatrics. 2004 Apr;59(4):26, 29-30

Peripheral arterial disease (PAD) is a manifestation of the atherosclerotic process and is associated with an increased risk of cerebrovascular disease, cardiovascular disease, and death. Clinicians should

consider screening both asymptomatic and symptomatic patients with the ankle-brachial index, a test with a high sensitivity and specificity. For those patients with PAD, atherosclerotic risk factors (such as smoking, dyslipidemia, hypertension, and diabetes mellitus) should be aggressively treated. In addition to exercise therapy, there is evidence available to support the use of aspirin, clopidogrel, lipid-lowering agents, pentoxifylline, and cilostazol.

## Analysis of the effects of phosphodiesterase type 3 and 4 inhibitors in cerebral arteries.

Reference: Eur J Pharmacol. 2004 Apr 5;489(1-2):93.

Inhibitors of phosphodiesterases 3 and 4, the main cyclic AMP (cAMP) degrading enzymes in arteries, may have therapeutic potential in cerebrovascular disorders. We analysed the effects of such phosphodiesterases in guinea pig cerebral arteries with organ bath technique and cyclic nucleotide assays. Guinea pig and human cerebral arteries were used for phosphodiesterase assays. Cilostazol (6-[4-(1-cyclohexyl-1H-tetrazol-5-yl)butoxy]-3,4-dihydro-2(1H)-quinolinone), a phosphodiesterase 3 inhibitor, was compared to conventional phosphodiesterase 3 and 4 inhibitors. Phosphodiesterases 3 and 4 were the major contributors to total cAMP hydrolysis in the arteries examined. The phosphodiesterase 3 inhibitors additionally attenuated cyclic GMP (cGMP) hydrolysis, but relaxant responses were not dependent on an intact endothelium or on the nitric oxide-cGMP pathway. Conversely, the phosphodiesterase 4 inhibitor used was endothelium-dependant and affected by cGMP levels. This suggests that phosphodiesterase 3 inhibitors are still effective under conditions with possible dysfunctional nitric oxide-cGMP pathway, such as in ischemic stroke or cerebral vasospasm.

## Recovery of platelet function after withdrawal of cilostazol administered orally for a long period.

Reference: J Atheroscler Thromb. 2003;10(6):348-54

To clarify the recovery of platelet function after abrupt withdrawal of cilostazol, we studied platelet function and cilostazol concentration in elderly who received cilostazol, 100 mg twice a day (200 mg/day), for a long period. After interviewing the time of final cilostazol intake, platelet aggregability was determined with an aggregometer using four different concentrations of adenosine-5'-diphosphate as an inducer, which showed

the grading curve (GC) type and platelet aggregatory threshold index (PATI). Serum cilostazol concentration was also determined by high-performance liquid chromatography. The GC type and PATI showed suppressed platelet function until 15 hours after withdrawal in half of patients. Bleeding time measured by the Simplate method was prolonged within 4 hours, but recovered by 12 hours after the withdrawal. Some serum cilostazol concentrations were still high 15 hours after withdrawal, while platelets were inhibited even in patients with low serum concentration of cilostazol. In the group receiving the drug for less than 6 months, PATI correlated with serum cilostazol concentration, but platelets in the long-term administration group (more than 48 months) were suppressed at the low serum cilostazol concentration. These findings indicated that platelet function recovered within 12-16 hours after withdrawal in these patients.

## **The antithrombotic profile of aspirin. Aspirin resistance, or simply failure?**

Reference: Thrombotic Journal 2004; 2(1): 1.

It is not surprising that a hypercoagulable state occurs in the plasma in acute coronary syndromes, as indicated by blood prothrombotic markers or by the presence of new cardiovascular events in the face of powerful antithrombotic therapy. Inflammation can have a prothrombotic effect through the increase of tissue factor, platelet reactivity or acute phase reactant proteins such as fibrinogen, or through a decrease in fibrinolysis by increasing the level of plasminogen activator inhibitor-1 [PAI-1].

Locally, thrombin is not only involved in coagulation; it has pro-inflammatory activity. Thrombin can activate receptors on platelets and the vascular endothelium, leading to inflammation and tissue injury. Activated platelets express CD40L and induce endothelial cells to secrete chemokines and to express adhesion molecules, indicating that platelets could initiate an inflammatory response of the vessel wall. Interesting, it has recently been shown that besides their specific activity, lipid-lowering drugs, the novel group of antidiabetic drugs thiazolidinediones, and angiotensin-converting enzyme inhibitor, all exhibit anti-inflammatory properties. Their clinical benefits may to some extent derive from lowering inflammation.

The underlying inflammation of atheromata in acute coronary syndromes could be the basis of failure of intensive antithrombotic therapy. COX-2 inhibition may decrease athero-inflammation, reducing monocyte infiltration and improving vascular cell function and plaque stability, resulting in a decrease of coronary

athero-thrombotic events. In our hands, the combination of a preferential COX-2 inhibitor, meloxicam, plus heparin and aspirin, proved superior to heparin and aspirin alone for reducing coronary thrombotic events in patients with acute coronary syndromes without ST-segment elevation.

In conclusion, aspirin resistance depends on circumstances independent of aspirin and could more aptly be termed aspirin failure. This is supported by the fact that increasing doses of aspirin can completely inhibit platelet aggregation in patients who are unresponsive or only partially responsive to aspirin [cited by]. Otherwise, thrombin generated at the endothelial lesion can induce platelet activation, which is not affected by aspirin.

All these findings indicate that, in acute coronary syndromes, there is a strong pro-clotting activity in the complicated atheroma. This activity is augmented by the underlying inflammation, which in several circumstances can overwhelm the inhibitory effects of single or combined anti-thrombotic drugs, including aspirin. Thus, the underlying endothelial and/or atheroma inflammation in coronary syndromes could explain why the antiplatelet effect of aspirin fails, irrespective of its anti-aggregating capacity or the urinary levels of thromboxane metabolites.

Biochem Biophys Res Commun. 2004 Jan 9;313(2):405-9.

### **Branched-chain amino acids as a protein- and energy-source in liver cirrhosis.**

Protein-energy malnutrition (PEM) is a common manifestation in cirrhotic patients with reported incidences as high as 65-90%. PEM affects largely the patients' quality of life and survival. Thus, diagnosis of and intervention for PEM is important in the clinical management of liver cirrhosis. Supplementation with branched-chain amino acids (BCAA) is indicated to improve protein malnutrition. As an intervention for energy malnutrition, frequent meal or late evening snack has been recently recommended. Plasma amino acid analysis characterizes the patients with liver cirrhosis to have decreased BCAA. Such reduction of BCAA is explained by enhanced consumption of BCAA for ammonia detoxication and for energy generation. Supplementation with BCAA raises in vitro the synthesis and secretion of albumin by cultured rat hepatocytes without affecting albumin mRNA expression. BCAA recover the impaired turnover kinetics of albumin both in rat cirrhotic model and in cirrhotic patients. Longer-term supplementation with BCAA raises plasma albumin, benefits quality of life issues, and finally improves survival in liver cirrhosis. Recent interests focused on the timing of administration of BCAA, since daytime BCAA are usually consumed by energy generation for physical exercise of skeletal muscles. Nocturnal BCAA seem to be more favorable as a source of protein synthesis by giving higher nitrogen balance. This minireview focuses on the basic and clinical aspects of BCAA as a pharmaco-nutritional source to control PEM in liver cirrhosis.

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