

# TOP Journal Club

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## Management of thrombotic and cardiovascular disorders in the new millenium.

Reference: Clin Appl Thromb Hemost. 2003;9(2):101-8

Anticoagulants and antithrombotic drugs have played a key role in the prophylaxis, treatment and surgical/interventional management of thrombotic and cardiovascular disorders. There are several newer drugs which are currently developed for the anticoagulant management of cardiovascular diseases in both the medical and surgical indications. These include the low molecular weight heparins (LMWHs), antithrombin agents such as the Hirudin, Hirulog and Argatroban and indirect and direct anti-Xa drugs, represented by Pentasaccharide (Arixtra) and DX 9065a, respectively. Several other agents such as the natural and recombinant anti-Xa drugs and anti-tissue factor agents are also developed. The antiplatelet agents include Clopidogrel, Cilostazol, Anplag and GP IIb/IIIa inhibitors. For the subcutaneous indications, unfractionated heparin is gradually replaced by the low molecular weight heparins (LMWHs). LMWHs such as the Enoxaparin and Dalteparin are commonly used for the management of acute coronary syndrome. These drugs have been approved for the treatment of unstable angina and are currently undergoing rigorous trials for interventional indications. Arixtra is also developed for various subcutaneous indications. However, it exhibits lower anticoagulant effects and may not be optimal for intravenous and interventional purposes. At a higher dosage when administered intravenously the LMWHs produce varying degrees of anticoagulation at relatively lower activated clotting times (150-200). Several studies in vascular and cardiovascular interventions have shown that even at a relatively lower anticoagulant level the LMWHs are as effective as unfractionated heparin at the recommended dosages which produce a relatively higher level of anticoagulation (ACT > 200 secs.). Thus, these agents are currently developed for interventional and surgical indications. It should be emphasized that different LMWHs produce different degrees of anticoagulation and should therefore be individually optimized for a given interventional or surgical purposes. At a relatively high dosage the levels of LMWHs can be measured by using the ACT and APTT. When administered with such GP IIb/IIIa inhibitors as the Abciximab, Aggrastat or Eptifibatide, these drugs may require dosage adjustment. However, since the

introduction of the front loading of Clopidogrel, the unqualified use of GP IIb/IIIa is debated. LMWHs will find expanded indications in both the medical and surgical management of patients with cardiovascular disorders including atrial fibrillation and congestive heart failure. The only approved anti-Xa drug is represented by a synthetic heparinomimetic, namely, Arixtra. This drug is given for the prophylaxis of post orthopedic indications. This agent is undergoing additional clinical trials in the management of coronary artery diseases. Because of the dependence on antithrombin III (AT) and the sole anti-Xa effects, it has a narrow therapeutic index and its efficacy in this indication may be limited. Additional clinical trials are needed at this time to validate the clinical potential of this drug. The antithrombin agents (Hirudin, Hirulog and Argatroban) were initially developed for arterial indications. However, these agents are approved as a substitute anticoagulant in patients with heparin induced thrombocytopenia (HIT) and PCI. Currently an of these agents are being developed for surgical and interventional use. However, since there is no available antidote at this time, the development is somewhat limited. The antithrombin agents may be useful in patients with HIT which require further clinical validation. Many other anti-Xa agents are also developed. Most of these can be given parenterally. However, the clinical data is somewhat limited. Similarly, several of the new antiplatelet drugs can be administered parenterally and may be useful in CAD. Since most of these newer anticoagulant and antithrombotic drugs are mono-therapeutic their therapeutic index is rather limited. Only in combination these agents can mimic heparins. At this time it is safe to state that heparin and its LMW derivatives will remain the anticoagulant of choice for cardiovascular indications until these newer agents have been validated in extended clinical trials in polytherapeutic settings.

## Cilostazol Prevents TNF- $\alpha$ -induced Cell Death by Suppression of PTEN Phosphorylation and Activation of Akt/CREB Phosphorylation.

Reference: J Pharmacol Exp Ther. 2003 Jun 13

This study examines the signaling mechanism by which cilostazol prevents neuronal cell death. Cilostazol (0.1 ~ 100 micro M) prevented TNF- $\alpha$ -induced decrease in viability of SK-N-SH and HCN-1A cells, which was antagonized by 1 micro M iberiotoxin, a maxi-K channel blocker. TNF- $\alpha$  did not suppress the viability of the U87-MG cell, a PTEN-null glioblastoma cell, but it did decrease viability of U87-MG cells transfected with expression vectors for the sense PTEN, and this

decrease was also prevented by cilostazol. Cilostazol as well as NS-1619 and BMS 204352, maxi-K channel openers, prevented increased DNA fragmentation evoked by TNF-alpha, which were antagonizable by iberiotoxin. TNF-alpha-induced increased PTEN phosphorylation and decreased Akt/CREB (cyclic AMP response element binding protein) phosphorylation were significantly prevented by cilostazol, those of which were antagonized by both iberiotoxin and paxilline, maxi-K channel blockers. The same results were evident in U87-MG cells transfected with expression vectors for sense PTEN. Cilostazol increases the K(+) current in SK-N-SH cells by activating maxi-K channels without affecting the ATP-sensitive K(+) channel. Thus, our results for the first time provide evidence that cilostazol prevents TNF-alpha-induced cell death by suppression of PTEN phosphorylation and activation of Akt/CREB phosphorylation via mediation of the maxi-K channel opening.

### **Effect of cilostazol on impaired vasodilatory response of the brachial artery to ischemia in smokers.**

Reference: J Atheroscler Thromb. 2003;10(2):93-8.

The vascular endothelial function of smokers is known to be impaired. This study investigated whether cilostazol could improve the vasodilatory response of the brachial artery to ischemia, an indicator of endothelial function, in ten male smokers. Endothelium-dependent vasodilatation and endothelium-independent vasodilatation of the brachial artery were measured in 11 male non-smokers and 20 male smokers with matching age and weight. The results showed that the vasodilatory response to reactive hyperemia was significantly smaller in the smokers (4.8 +/- 1.6%) when compared to that in the non-smokers (7.6 +/- 2.5%) (p = 0.0013). However, no significant difference in the vasodilatory response to isosorbide dinitrate was observed between the two groups. In addition, there were no significant differences in serum lipid, Lp (a), or blood homocysteine between the smokers and non-smokers. When 150 mg/day of cilostazol was administered for two weeks, the vasodilatory response to reactive hyperemia significantly improved (4.2 +/- 1.2% to 7.8 +/- 3.5%, p = 0.0032). The increased vasodilatory response to reactive hyperemia by cilostazol was reduced after cessation of the drug (4.5 +/- 1.5%). These findings suggest that cilostazol improves vascular endothelial dysfunction in smokers.

### **Characteristics of attenuating effects of rebamipide, an anti-ulcer agent, on oxidative burst of human neutrophils.**

Reference: J Pharmacol Sci. 2003 Feb;91(2):153-7.

The aim of this study was to characterize the effects of rebamipide on the oxidative burst of human neutrophils. The neutrophil oxidative burst was measured in the presence of rebamipide and cimetidine using lucigenin- or luminol-dependent chemiluminescence (LgCL or LmCL). Rebamipide inhibited the LmCL response stimulated with opsonized zymosan, 12-myristate 13-acetate phorbol, and calcium ionophore in a dose-dependent manner, but the LgCL response was inhibited when neutrophils were stimulated with opsonized zymosan. LmCL response was also dose-dependently attenuated by rebamipide even in the presence of cimetidine. Thus, addition of rebamipide to H(2)-receptor antagonists can be considered for the treatment of gastric mucosal injury associated with oxidative stress.

### **Cytoprotective Effects of Rebamipide and Carteolol Hydrochloride against Ultraviolet B-Induced Corneal Damage in Mice.**

Reference: Invest Ophthalmol Vis Sci. 2003 Jul;44(7):2980-5.

**PURPOSE.** To analyze whether rebamipide (REB) and carteolol hydrochloride (CH) protect against UVB-induced corneal damage in mice. **METHODS.** BALB/c mice topically pretreated with REB (1 and 10 mM) or CH (1, 10, and 100 mM) were exposed to ultraviolet (UV) B light at 416 micro W/cm(2). To evaluate corneal damage, mire irregularity was graded, and the haze index was estimated by using digitized corneal images. The formation of oxidized DNA in the corneal epithelium resulting from UVB exposure was estimated by using quantitative immunohistochemistry for 8-hydroxy-2-deoxyguanosine (8OHdG index). To analyze the mechanism of cytoprotection by REB and CH against UVB-induced cell damage, the UV absorption spectrum in these agents was evaluated by spectrophotometry, and their hydroxyl radical scavenging effect was evaluated by the electron spin resonance (ESR) spin trapping technique with Fenton system hydroxyl radical generation. **RESULTS.** Seventy-two hours after UVB exposure, the severity of mire irregularity, haze index, and 8OHdG index were significantly lower in mice pretreated with 10 mM (P < 0.05, P < 0.05, and P < 0.01, respectively) of REB and in mice pretreated with 10 mM (P < 0.05, P < 0.01, and P < 0.01, respectively) and 100 mM (P < 0.01, P < 0.01, and P < 0.01, respectively) of CH compared with mice treated with vehicle. The absorption spectrum of REB overlapped with the UVB wavelength, and that of CH overlapped partially. The ESR spin signal corresponding to the hydroxyl radical was reduced by the addition of REB or CH. **CONCLUSIONS.** REB and CH attenuate UVB-induced corneal damage, which may be partly responsible for their sunscreens and hydroxyl radical scavenging effects.