

# TOP Journal Club

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## The phosphodiesterase 3 inhibitor cilostazol dilates large cerebral arteries in humans without affecting regional cerebral blood flow.

Cilostazol, an inhibitor of phosphodiesterase (PDE) type 3, is used clinically in peripheral artery disease. PDE3 inhibitors may be clinically useful in the treatment of delayed cerebral vasospasm after subarachnoid hemorrhage. The authors present the first results on the effect of cilostazol on cerebral hemodynamics in normal participants. In this double-blind, randomized, crossover study, 200 mg cilostazol or placebo was administered orally to 12 healthy participants. Cerebral blood flow was measured using  $^{133}\text{Xe}$  inhalation and single photon emission computerized tomography. Mean flow velocity in the middle cerebral arteries (VMCA) was measured with transcranial Doppler, and the superficial temporal and radial arteries diameters were measured with ultrasonography. During the 4-hour observation period, there was no effect on systolic blood pressure ( $P = 0.28$ ), but diastolic blood pressure decreased slightly compared with placebo ( $P = 0.04$ ). VMCA decreased 21.5  $\pm$  5.7% after cilostazol and 5.5  $\pm$  12.2% after placebo ( $P = 0.02$ , vs. placebo), without any change in global or regional cerebral blood flow. The superficial temporal artery diameter increased 17.6  $\pm$  12.3% ( $P < 0.001$  vs. baseline) and radial artery diameter increased 12.6  $\pm$  8.6% ( $P < 0.001$  vs. baseline). Adverse events, especially headache, were common. The findings suggest that cilostazol is an interesting candidate for future clinical trials of delayed cerebral vasospasm.

*J Cereb Blood Flow Metab.* 2004 Dec;24(12):1352-8

## Effect of remnant-like particle on shear-induced platelet activation and its inhibition by antiplatelet agents.

Remnant-like particles (RLPs) have been reported to promote atherosclerosis and to have effects on platelet function. We studied the effects of RLP on shear-induced platelet activation and their inhibition by antiplatelet agents in vitro. RLP were separated using two monoclonal antibodies, anti apo B-100

and anti apo A-I. These RLP fractions were added to whole blood (WB) or platelet-rich plasma (PRP) in serial dilution of 1, 10 or 100 mug RLP triglyceride (TG) per ml of total sample volume. These samples were incubated, and then stimulated with a high shear stress of 108 dyn/cm<sup>2</sup>. Shear-induced platelet aggregation (SIPA) was calculated from the percentage of single platelet loss. P-selectin expression on platelet surface and platelet-derived microparticle (PMP) generation were measured before and after stimulation with shear stress using flow cytometer. SIPA was significantly enhanced by RLP in WB but not in PRP. This enhancing effect was not dose-dependent and was greatest at 10 mug TG/ml. P-selectin expression induced by shear stress was only enhanced by RLP at a concentration of 100 mug TG/ml in both WB and PRP, while generation of PMP induced by shear stress was only enhanced by RLP at a concentration of 100 mug TG/ml in WB. Aspirin inhibited only the enhancement of SIPA by RLPs, while cilostazol inhibited the enhancement of not only SIPA but also p-selectin expression and PMP generation by RLPs.

*Thromb Res.* 2005;115(3):211-8.

## Early and late recurrence of ischemic lesion on MRI: evidence for a prolonged stroke-prone state?

**BACKGROUND:** Based on previous observations of a high rate of ischemic lesion recurrence on diffusion-weighted imaging (DWI) within 1 week after an acute ischemic stroke, the authors hypothesized that silent new ischemic lesions are common between 1 week and 90 days after index stroke and that early lesion recurrence may be associated with late lesion recurrence. **METHODS:** The authors studied 80 acute ischemic stroke patients who had initial MRI performed within 48 hours, and follow-up scans at 5 days and at 30 or 90 days after onset. Early lesion recurrences were defined as new ischemic lesions on 5-day DWI, and late lesion recurrences were defined as those on 30- or 90-day DWI or fluid attenuation inversion recovery image. Early lesion recurrence occurring outside the initial perfusion deficit was termed distant lesion recurrence. **RESULTS:** Late lesion recurrence occurred in 26%, more frequently observed on 30-day MRI than 90-day MRI ( $p = 0.016$ ). Early lesion recurrence (OR 4.0; 95% CI 1.3 to 11.7) and distant early lesion recurrence (OR 6.9; 95% CI 1.5 to 32.2) were independently associated with late lesion recurrence by multiple logistic

regression analyses. **CONCLUSIONS:** There may be a continued risk for recurrent ischemic lesions in the weeks following the clinically symptomatic stroke. Future studies are needed to investigate whether MRI-defined ischemic lesion recurrences predict subsequent clinical recurrence and thus may be a potential surrogate endpoint in stroke secondary prevention trials.

*Neurology. 2004 Dec 28;63(12):2261-5*

## Protecting the brain: the search for a clinically effective neuroprotective drug for stroke.

The idea that it should be possible to develop a neuroprotective drug that protects the brain from some of the consequences of an acute ischaemic stroke has been in existence for some time and has developed from our increasing knowledge of the biochemical consequences of an acute ischaemic episode. A variety of drugs have been developed to interfere with these biochemical changes. However, while many of these compounds have been shown to be efficacious in animal models of stroke, none has succeeded in clinical trials and reached the market in the Western world. Partly as a result of these failures, guidelines have been published and further extended that detail criteria that should be met before a novel compound is progressed to clinical investigation. These guidelines are reviewed herein, and the author suggests the probability that none of the compounds that have previously failed clinically would have fulfilled the current selection criteria for advancement to clinical trial. It is proposed that NXY-059 (Cerovive) is the first neuroprotective agent to reach the clinical trial phase that meets all the suggested guidelines for neuroprotective drug development, and the preclinical profile of this compound is reviewed.

*Crit Rev Neurobiol. 2004;16(1-2):91-7*

## Anti-adhesion molecule strategies as potential neuroprotective agents in cerebral ischemia: a critical review of the literature.

Despite recent advances in the understanding of the pathophysiology of cerebral ischemia, current approaches attempting to prevent ischemic brain damage after an acute stroke remain quite inadequate. Today, ischemic stroke remains the third leading cause of death in industrialized

nations, and the leading cause of disability requiring long term institutional care in the U.S and other industrialized nations. While one treatment, tissue plasminogen activator, has shown efficacy in clinical trials, safety concerns limit its role in clinical practice to a narrow time window of use. Acute cerebral ischemia has been shown to evoke a profound and deleterious upregulation of the inflammatory response, initiated within the cerebral microvasculature. Recently, research efforts have focused on targeting individual components of the inflammatory cascade, such as leukocyte activation and adhesion, in an attempt to develop potential neuroprotective agents. While these strategies have shown promise preclinically, clinical trials have yet to show clear benefit. Here, we review the current understanding of the pathophysiologic consequences of acute cerebral ischemic injury. Additionally, we discuss the role of the inflammatory cascade, with specific attention given to the deleterious role played by leukocyte activation and adhesion in stroke. Finally, relevant efforts to translate these basic science observations into clinical efficacy in acute stroke trials are critically reviewed.

*Inflamm Res. 2004 Oct;53(10):497-508*

## Optimum oral antiplatelet therapy for vascular disease.

Aspirin is the recommended oral first-line antiplatelet therapy for patients with ST-segment elevation myocardial infarction. Aspirin or clopidogrel is recommended for those with initial transient ischemic attack (TIA)/ischemic stroke, chronic stable angina, or peripheral arterial disease; aspirin plus clopidogrel should be used for those with non-ST-segment elevation acute coronary syndrome. For second-line therapy, the combination of aspirin and clopidogrel is recommended for recurrent acute coronary syndrome. The combination of aspirin and extended-release dipyridamole is recommended for patients with recurrent TIA/ischemic stroke in the absence of known coronary artery disease. Further studies are needed before making firm recommendations on the management of patients with recurrent TIA/ischemic stroke and known coronary artery disease.

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