Cilostazol, a Phosphodiesterase III Inhibitor: Future Prospects for Atherosclerosis

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Pharmacological properties of cilostazol

Cilostazol was released in Japan and other Asiatic countries in 1988 and approved in the United States of America in 1999, for clinical treatment of intermittent claudication caused by POAD which is an important marker of systemic atherosclerosis. Study results demonstrate the superiority of cilostazol in comparison to placebo and pentoxifylline to increase walking distance without pain in 50% of the patients, and the maximum walking distance in 64% of the patients, thus improving quality of life.

This medication is an antithrombotic antiplatelet agent with vasodilation action. There is no evidence that it prolongs bleeding time when compared to acetylsalicylic acid (ASA), clopidogrel or ticlopidine, or even various combinations of these drugs. It is a potent phosphodiesterase 3 selective inhibitor, which increases cyclic adenosine monophosphate (cAMP) in the thrombocytes and smooth muscle cells, and diminishes intracellular calcium which, in turn, causes cellular relaxation and vasodilation. Cyclic AMP is one of the regulators of inflammatory and immunological reactions.

It is metabolized via the cytochrome P450, primarily the isoenzyme CYP3A4, and is excreted by the kidneys. It should not be used concomitantly with ketoconazole, itraconazole, miconazole, fluconazole, fluvoxamine, fluoxetine, nefazodone, sertraline, omeprazole, erythromycin, diltiazem and quinidine; if indicated should be given in reduced dosages.

The treatment depends on gender, age, smoking, presence of diabetes mellitus (DM), the concomitant use of betablockers or calcium antagonists. Studies have shown that it is safe to use cilostazol for patients with acute myocardial infarction (AMI) despite the increased cardiac index, coronary flow and contractility.

The most common collateral effects include headache, tachycardia, palpitations, soft stools and diarrhea. In two studies it was necessary to interrupt the use of cilostazol due to headaches in 1.7% of the patients in relation to 1.3% in those treated with placebo, while suspension for other causes was similar between the groups. In the case of chronic liver disease, Child-Pugh classes B and C, it should be used with caution. It is not advised in the case of congestive heart failure or for patients with left ventricle ejection fractions less than 40%.

The effect of cilostazol in the prevention of thrombotic complications and restenosis

The accumulation of cAMP, caused by cilostazol through the diminished phosphodiesterase 3 activity, initiates a series of events which include regulation of the tumor suppressor genes p53 and p21 and hepatocyte growth factor (HGF). The increased suppression of the p53 protein in the cellular cycle induces apoptosis in the smooth vascular muscle cells, causing an antiproliferative effect. HGF stimulates the rapid endothelial cell regeneration that inhibits neointimal formation by two mechanisms: suppressing the growth of abnormal smooth vascular muscle cells and improved endothelial function (Figure 1). These mechanisms could be responsible for preventing restenosis after coronary stenting.

The incidence of thrombosis and restenosis after coronary stenting is still elevated, even with pharmacological devices, and thrombotic events remain the primary cause of death after percutaneous transluminal coronary angioplasty. In a cohort of 2229 patients who received stents coated with sirolimus or paclitaxel and were followed for nine months, the cumulative incidence of thrombosis was 1.3%, substantially higher than the rate referred in larger clinical trials (0.4% in one year for sirolimus and 0.6% in nine months for paclitaxel). The follow-up timeframe was nine months.

Cilostazol demonstrated results similar to ticlopidine, when associated with ASA, in the inhibition of platelet aggregation induced by shear stress, after coronary intervention in patients with AMI and follow-up for three months.

It also demonstrated analogous performance to ticlopidine in relation to the restenosis rate, both associated with ASA, in a multicenter study with 397 patients submitted to elective coronary stent placement procedures and followed for six months. In the extended follow-up of nine months, the performance of cilostazol was significantly better in relation to the number of revascularization surgeries required for target lesions.

The first study that recognized and compared cilostazol and clopidogrel, used in conjunction with ASA, demonstrated that both had a similar effect in the prevention of thrombotic...
complications. No significant differences were found between cilostazol and clopidogrel for post AMI or non pharmacological stent implants for long, multiple and complex coronary lesions. The study lasted for thirty days and evaluated 689 patients.

The effect of cilostazol on dyslipidemia

Even though the cholesterol contained in the low density lipoproteins (LDL) continues to be the main target in the treatment of dyslipidemia, the increase of HDL and reduction of triglycerides (TG) have proven to be very important in reducing cardiovascular risk, particularly for people with DM. While the isolated and fasting levels of HDL and TG are important, recent studies have shown that evaluation of triglyceride rich lipoproteins (VLDL) and cholesterol contained in very low density lipoproteins - VLDL - during the postprandial period is more effective to verify the risk of coronary artery disease (CAD) or other atherosclerotic alterations.

Generally, dietary sources of fat exceed the daily recommendations and the tissues are mobilized to accumulate more nutrients than required. Zilversmit, in 1979, demonstrated that atherogenesis can occur after eating. Other clinical studies reinforce this idea and suggest that the inefficient TG removal during the postprandial period can promote atherosclerosis. It is important to understand that the postprandial response does not only represent the influx of TG from the diet in the circulation, but also a period when the lipoprotein composition is significantly altered. The dimension of remodeled lipoproteins, that occurs during lipemia is directly related to the duration and size of the postprandial triglyceridemia. Additionally, lipemia after eating promotes catabolism of HDL and its low blood concentration is associated with increased risk of CAD. Postprandial hypertriglyceridemia stimulates the formation of small, dense LDL that are very atherogenic and increase the risk of CAD by four to six times.

Cilostazol diminished the concentration of remaining VLDL and chylomicrons by 20%, increased HDL and diminished TG in 874 patients with POAD, during a randomized multicenter study, controlled with pentoxifylline and placebo with six months of follow-up. In 189 individuals with POAD and without hyperlipidemia, cilostazol reduced TG by 15% and increased HDL by 9.5%, in a double blind multicenter study, controlled with placebo and twelve weeks of follow-up. It also improved postprandial lipemia in 112 patients with type 2 DM or glucose intolerance, controlled with placebo during twelve weeks of follow-up.

The effect of cilostazol on inflammatory markers

Atherosclerosis is characterized by endothelial lesions, adhesion of mononuclear leukocytes, migration and proliferation of smooth muscle cells, as well as extracellular matrix deposition. It is considered as an inflammatory disease and a pathological view point all the development stages of atherosclerotic plaque -- formation, growth and complication -- can be considered inflammatory responses to the endothelial lesion. This justifies not only the aggressive handling of the modifiable risk factors but also the treatment of the causal lesion and stabilization of other lesions.

Various adhesion molecules such as the vascular cell adhesion molecule 1 (VCAM-1) and monocyte chemoattractant protein-1 (MCP-1), have been detected in atherosclerotic lesions, promoting an interaction between the endothelial surface and the circulating leukocytes, mediating their recruitment and accumulation on the intima of the blood cell wall. VCAM-1 has an important role in mediating the selective adhesion of mononuclear leukocytes to the vascular endothelial and is a marker of early onset atherosclerosis. MCP-1 is a chemokine which also has an important role in mediating the recruitment of monocytes in the atherosclerotic lesions. Therefore, eliminating the expression of these adhesion molecules could be a strategy to prevent atherogenesis.

TNF-α (tumor necrosis factor alpha) is a cytokine that is implicated not only in the induction of endothelial apoptosis but also in the progression of atherosclerotic lesions. Interleukin-6 (IL-6) is a pro-inflammatory cytokine produced by various cell types including macrophages, lymphocytes and endothelial cells, which inhibits lipoprotein lipase, an important enzyme in the catabolism process of triglyceride rich lipoproteins and stimulates the secretion of hepatic TG.

Cilostazol suppressed cytokine production in a mastocyte culture. It also blocked the production and expression of MCP-1 induced by TNF-α, in culture of endothelial cells taken from a human umbilical cord. It inhibited VCAM-1 in a culture of endothelial cells taken from a human umbilical cord via suppression of the nuclear transcription factor kappa B.

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In rats it diminished the superoxide action, demonstrating a possible antioxidant and TNF-α effect\(^5\), it also inhibited the TNF-α in a culture of human neuroblastoma cells\(^6\).

Additionally, cilostazol increased the lipoprotein lipase activity in a culture of aorta cells from rats\(^7\), diminished IL-6 in patients submitted to revascularization procedures for POAD\(^8\) and inhibited IL-6 in a study with POAD patients controlled with pentoxifylline and placebo\(^9\).

The effect of cilostazol on nitric oxide and apoptosis

Nitric oxide (NO) provides a variety of functions to protect vessels such as vasodilation, inhibition of the migration and proliferation of smooth vascular muscle cells and stimulation of endothelial growth, preserving endothelial function; it is also involved in the regulation of coronary circulation\(^10\).

Apoptosis, or programmed cell death, is an important tissue function to maintain homeostasis through the elimination of undesired and/or harmful cells. It is associated with the development of atherosclerotic plaque and occurs with greater frequency in advanced plaques\(^11\).

Among the factors responsible for apoptosis are oxidative stress\(^12\) and the B-cell leukemia/lymphoma 2 (Bcl-2) gene family\(^13\). The Bcl-2 gene was originally identified as an oncogene of human follicular lymphoma\(^14\) and later, was suggestive of suppressing cell death by apoptosis in a variety of in vitro systems and cellular lineages, promoting cellular survival after cerebral ischemia in rats\(^15\). The Bcl2 associated X protein (BAX) is a member of the Bcl-2 family that, in opposition, promotes cell death\(^16\).

Cilostazol increased the NO expression in cell cultures\(^17, 18\) and rats\(^19\), positively altered oxidative stress\(^20, 21\), inhibited apoptosis induced by lipopolysaccharides; it diminished BAX gene levels and increased Bcl-2 gene levels, in cultures of endothelial cells taken from a human umbilical cord\(^22\). It also diminished cerebral stroke in association with apoptosis inhibition and oxidative cellular death in rats submitted to focal cerebral ischemia\(^23\).

Conclusion

The pharmacological treatment of atherosclerosis can diminish the rate of progression of the disease and in certain cases can also cause involution\(^24\).

Cilostazol acts as a vasodilator, antithrombotic antiplatelet agent. This drug promotes lower TG levels, increases HDL in patients with POAD\(^25\), improves postprandial lipemia in patients with DM\(^26\), increases NO expression, has a positive effect on apoptosis, prevents thrombosis after stenting and has demonstrated the ability to interfere in various stages of the atherosclerotic process.

These effects can make cilostazol an important option in the treatment of atherosclerosis. Further controlled clinical trials and studies are required to evaluate these other effects, as well as its already established role as a peripheral vasodilator.

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Clinical Update

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