Cilostazol for Secondary Prevention of Stroke: Should the Guidelines Perhaps Be Extended?

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Cilostazol belongs to the new generation antiplatelet agents that have been introduced and studied regarding a potential role in cardiovascular disease prevention or treatment. Although data on peripheral artery disease are sufficient, and the drug has been recommended as first line treatment for intermittent claudication, it has not been approved nor recommended as far as cerebrovascular events are concerned. However, a great volume of randomized as well as pooled data has been published during the last years. Therefore, this review aims to describe the basic mechanisms of cilostazol's action as well as to present all recent clinical data in order to conclude on whether official guidelines should be extended.

Key Words: Stroke, Secondary prevention, Guideline

INTRODUCTION

Cilostazol, a cyclic adenosine monophosphate (cAMP) phosphodiesterase inhibitor, has been introduced as a new antiplatelet agent due to its pleotropic actions, including vasodilation and inhibition of platelet aggregation [1-3]. It has been demonstrated that cilostazol reduces post-procedural in-stent restenosis after coronary and carotid artery stenting as well as after endovascular procedures for peripheral artery disease [4,5]. Several studies have also highlighted the superiority of this agent compared to other antiplatelets concerning the secondary prevention of stroke as well as the protection against hemorrhagic events [6]. However, recent guidelines do not include any recommendation concerning the standardized use of cilostazol alone or in combination with other antiplatelets, prior or after cerebrovascular events, for primary or secondary protection.

Therefore, this review aims to present and discuss recent data regarding the role of this agent in secondary stroke prevention in order to produce useful conclusions for everyday clinical practice.

ACTION OF CILOSTAZOL

Cilostazol decreases thromboxane formation by enhancement of the platelet/cAMP level [2,3], leading to a pleotropic action that includes: inhibition of platelet aggregation and vasodilation [1,3], vascular smooth muscle cell (VSMC) re-differentiation [7,8], an increase in heart rate and contractile force, and an improvement in lipid metabolism [9]. Moreover, the effect on cAMP levels results in upregulation of the anti-oncogenes p53 and p21, and hepatocyte growth factor [10]. This increase in p53 protein blocks cell cycle progression and induces apoptosis in VSMCs, leading to an antiproliferative effect. Furthermore, hepatocyte growth factor stimulates re-endothelization after vascular injury, inhibits abnormal VSMC growth, and improves endothelial function [10,11]. Additionally, recent data indicate

that cilostazol induces angiogenesis through the aforementioned pathways in vascular cells [12].

Recent experimental investigations have revealed that cilostazol has a neuroprotective effect against ischemic brain injury [13]. The neuroprotective potential is dependent on its anti-inflammatory and anti-apoptotic effects mediated by scavenging hydroxyl radicals, decreasing formation of tumor necrosis factor-α, and inhibition of poly (adenosine diphosphate-ribose) polymerase activity. In addition, increasing evidence indicates that cilostazol may offer endothelial protection via both the inhibition of lipopolysaccharide-induced apoptosis and induced nitric oxide (NO) production by endothelial NO synthase activation [14]. The breakdown of the barrier permeability of the blood brain barrier often accelerates the progression of diseases, such as cerebral ischemia [15]. However, cilostazol seems to reduce brain barrier dysfunction as well as the degree of intracerebral cell death [16]. Honda et al. [17] have shown that treatment with cilostazol significantly reduces the gray and white matter damage associated with permanent focal ischemia, in a rodent model. In this study, cilostazol significantly improved regional cerebral blood volume and flow in the peri-infarct area, increasing perfusion particularly in the ischemic penumbra. Finally, data indicate that this agent also prevents symptomatic cerebral vasospasm and improves major outcomes, including new cerebral infarctions [18].

Even in the case of hemorrhage, cilostazol has been found to be protective in animal models. This could be explained as previous studies have demonstrated that cilostazol does not prolong bleeding time when compared with aspirin, thienopyridines, or various combinations of these drugs [19]. Takagi and Hara [20] found that cilostazol prevented the hemorrhagic transformation induced by focal cerebral ischemia in mice treated with intravenous tissue plasminogen activator or warfarin via protecting endothelial cells and tight junction proteins. They also demonstrated that cilostazol attenuated collagenase-induced intracranial hemorrhage in mice. In vitro studies [17] have shown that endothelial cells, pericytes, tight junction proteins, adherence junction proteins, and the basement membrane, which are all components of the blood-brain barrier, are protected by the administration of cilostazol following collagenase injury. These results could suggest that cilostazol reduces the risk for hemorrhagic stroke by protecting the entire blood-brain barrier, concurring with other studies as well [21].

POOLED DATA ON SECONDARY PREVENTION OF STROKE

All these beneficial—experimentally proven—actions have been the main reason to initiate clinical trials in order to evaluate the role of cilostazol in everyday clinical practice. In a recent meta-analysis by Xie et al. [22], 24 randomized trials evaluating either dual or single antiplatelet therapies for the secondary protection after an ischemic stroke or transient ischemic attack (TIA) were included. In this pooled study of over 85,000 patients, long-term monotherapy was found to be a better choice than long-term dual therapy, with cilostazol showing the best risk-benefit profile for long-term secondary prevention after stroke or TIA. These results concur with another meta-analysis by Niu et al. [23], where cilostazol was found to be superior compared to other regimens in the long-term, regarding vascular events prevention and bleeding risk. Wang et al. [24] have also concluded that cilostazol is significantly more efficient than other therapies, improving overall stroke and hemorrhagic stroke risk in patients with previous stroke or TIA. However, it is important to underline that most of the pooled evidence available to date is based on studies evaluating mainly Asian populations, and this could be one of the reasons that this agent is not approved for treatment of cerebrovascular disease in USA yet. Therefore, future trials should focus in non-Asian patients in order to produce safer results.

When distinguishing the acute phase from the chronic phase of a stroke, Shi et al. [25] have found that cilostazol does not show any effect on major outcomes (including recurrence of infarction, hemorrhagic stroke or all-cause death) regarding the acute phase, compared to placebo or aspirin. However, when referring to the chronic phase of a stroke, cilostazol was associated with a significant reduction of recurrences as well as hemorrhagic events. Even regarding the risk of other vascular events after a stroke (including secondary stroke, myocardial infarction or vascular death), cilostazol has been found to be superior against aspirin (6.77% vs. 9.39%; risk ratio, 0.72; 95% confidence interval, 0.57 to 0.91) in recent systematic review [26]. Finally, this advantage of cilostazol compared to other regimens has been highlighted in other meta-analyses as well [6,27].

However, there is some pooled evidence available showing no special benefit using cilostazol. Recently, Kwok et al. [28] have evaluated the efficacy of different antiplatelet agents regarding secondary prevention after lacunar stroke. The purpose of this review was that lacunar stroke accounts for almost 25% of ischemic stroke although optimal antiplatelet regimen for prevention of stroke recurrence remained unclear in this subgroup of patients. The authors evaluated almost 17 trials and concluded that when compared with aspirin, other antiplatelets including cilostazol showed no consistent reduction in stroke recurrence. Moreover, Malloy et al. [29] compared several combinations

of antiplatelet treatment for secondary prevention against stroke and have found no difference of combinations regarding stroke prevention although cilostazol was associated with fewer hemorrhagic events compared to aspirin plus dipyridamole or aspirin plus clopidogrel. Hence, cilostazol's advantage concerning bleeding in this study was even higher than the advantage of other single antiplatelets (such as ticlopidine, triflusal or sarpogrelate).

GUIDELINES AND RECOMMENDATIONS

Regarding official recommendations, cilostazol has been approved by the USA Food and Drug Association (FDA) and it is recommended as a class 1 treatment for patients with peripheral artery disease and intermittent claudication, according to American Heart Association Guidelines [30]. However, it has not been approved by the FDA as a treatment in patients with stroke or other cerebrovascular disease and therefore, it has not been incorporated in the official recommendations for primary or secondary stroke prevention yet. According to the latest 2014 Guidelines on secondary stroke prevention [31], there was some evidence produced by randomized trials in Asian patients showing non-inferior results of cilostazol compared to aspirin regarding the reduction of stroke and bleeding events. However, as the authors underline [31], cilostazol has not been studied in non-Asian populations, so it is uncertain whether this effect is translatable to other groups. Therefore, the authors conclude that for patients with stroke or TIA attributable to 50% to 99% stenosis of a major intracranial artery, the data are insufficient to make a recommendation regarding the usefulness of clopidogrel alone, the combination of aspirin and dipyridamole, or cilostazol alone (Class IIb; Level of Evidence C).

CONCLUSION

Since the last published guidelines, several randomized and pooled data have shown the superiority of cilostazol over other antiplatelets regarding the secondary prevention of stroke or TIA. Although the drug has not been approved by FDA for stroke treatment yet, the volume of supportive data indicates that this agent should be incorporated in future recommendations. However, more randomized data from non-Asian populations are needed to support this.

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