REVIEW ARTICLE

Contribution to prevention of cerebral ischemia by cilostazol, a phosphodiesterase III inhibitor: a review

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ABSTRACT

This literature review aims at presenting the main possibilities for the clinical application of cilostazol in the central nervous system. Cilostazol, a selective phosphodiesterase type III inhibitor, increases adenosine 3',5'-cyclic monophosphate levels on platelets, endothelial and smooth muscle cells, having vasodilatory, antiplatelet and antithrombotic properties. Currently, it is the first-choice drug for intermittent claudication, due to peripheral occlusive vascular disease. In addition, there is evidence showing that cilostazol is efficacious in cerebral atherosclerotic process, resulting in increase of blood flow and volume and preventing infarctions, especially lacunar and recurrent, since it reduces cellular death due to apoptosis and oxidative stress in white and gray substances.

Keywords: Phosphodiesterase inhibitors, cerebral infarction, cerebral blood flow, cilostazol.

RESUMO

Esta revisão bibliográfica objetiva expor estas pesquisas sobre as ações do cilostazol no sistema nervoso central. O cilostazol é uma droga que demonstrou exercer inibição seletiva e potente da fosfodiesterase tipo III, ocasionando o aumento de adenosina cíclica -3',5'-monofosfato nas plaquetas, nas células endoteliais e nas células musculares lisas, sendo classificado como vasodilatador, antiagregante plaquetário e antitrombótico. É o fármaco de primeira escolha na

claudicação intermitente devido à doença arterial obstrutiva periférica. Além disso, há evidências de que o cilostazol é eficaz no processo aterosclerótico cerebral, promovendo aumento do fluxo e volume sangüíneos e prevenindo infartos, especialmente lacunares e recorrentes, por diminuir a morte celular devido à apoptose e ao estresse oxidativo nas substâncias branca e parda.

Palavras-chave: Inibidores de fosfodiesterase, infarto cerebral, fluxo sangüíneo cerebral, cilostazol.

Introduction

Reduced cerebral blood flow implies not only vascular dementia caused by multiple infarctions, but also other types of mental deterioration, including Alzheimer's disease.[1] White matter lesions, such as hypertension and cerebrovascular changes, are more common in old age, being responsible for cognitive decline and walking disorders.[2] Loss of myelin an axonal damage were identified in experimental chronic cerebral ischemia, induced by permanent occlusion of the common carotid artery in rats, whose model has been proposed for vascular dementia and circulatory lesions in the white matter.[3-5]

Suppression of microglia, which is activated by contact with neural damage, and mitigation of white matter lesions using an antiinflammatory drug (nimesulide) have been demonstrated in a previous study, suggesting the importance of inflammatory reaction in causing lesions in that brain region.[6] Microglia, playing a major role in development and remodeling of the central nervous system (CNS), followed by astrocytes, which form the glia and contribute to the blood-brain barrier, are the greatest sources of tumor necrosis factor alpha (TNF-α).[7] TNF-α, as a proinflammatory cytokine, induces formation of post-ischemia and loss of myelin.[8] On the other hand, death of oligodendroglial cells was reported as occurring after bilateral carotid occlusion in gerbils[9] and in transient global ischemia in rats.[10] Previous research studies demonstrated that the optic tract, submitted to chronic cerebral hypoperfusion, caused activation of microglial cells, exacerbating white matter lesions and producing reactive oxygen species, besides proinflammatory cytokines, such as TNF-α.[8]

There is accumulated evidence that oligodendroglial apoptosis in human brains is increased in white matter ischemic lesions, consisting of myelin degeneration, astrogliosis, microglia activation and loss of oligodendroglia.[11,12] Oligodendroglia are cells that form myelin sheaths in brain axons and are more likely to have oxidative stress than other glial cells, such as astrocytes,[13,14] causing apoptosis with activation of caspases, enzymes that are proapoptotic markers.[10]

Also, cells with *in situ* nick end labeling (TUNEL), a method to detect areas of deoxyribonucleic acid (DNA) that are eliminated during apoptosis,[15] and cytochrome c, which is an initial mediator of caspase activation, secreted by mitochondria during hypotonic lysis of cells,[16] are manifested is ischemia. Chronic cerebral hypoperfusion causes increase in glial fibrillary acidic protein (GFAP), a marker for astrocytes that is the intermediate filament only found in glial cells or that have glial origin,[17] and in anti-CD11b monoclonal antibody (OX-42), a marker of microglia in the optic tract, indicating microglia hyperactivation,[18] whereas 3',5'-cyclic nucleotide 3'-phosphodiesterase (CNPase), a marker of oligodendrocytes, is significantly reduced, suggesting increase in their death.[19]

Among the factors responsible for apoptosis is the family of B-cell-leukemia/lymphoma-2 (Bcl-2)

genes. The Bcl-2 gene has been suggested as suppressor of cell death due to apoptosis in a variety of *in vitro* systems and in cell lineages (reed). The X protein associated with Bcl (BAX) is a member of the Bcl-2 family that, on the contrary, causes cell death due to mitochondrial dysfunction and caspase activation.

The phosphatidylinositol 3-kinase/serine-threonine protein (PI3K/Akt) metabolic pathway plays a major role to regulate several cell functions, including growth, differentiation and apoptosis.[20] In addition, apoptosis contains protein kinase 2 (CK2), which is a transcription factor present in nucleus and cytoplasm that is regulated by calcium. It is involved in many metabolic processes related to cell growth and proliferation, catalyzed by phosphorilation of a large number of protein kinase.[21] On the other hand, there is phosphorilation of the phosphatase gene and tensin homologue deleted on chromosome 10 (PTEN), apoptosis controller through cell regulation and viability by caspase activation and inhibition of DNA-binding protein to cyclic adenosine 3',5'-monophosphate (CREB), a cascade activated by multiple growth factors and cytokines that regulate cell survival and growth.[22] CREB fosters cell survival, including neurons.[23]

Cilostazol pharmacology

Cilostazol is indicated for clinical treatment of intermittent claudication caused by peripheral occlusive arterial disease (POAD), a situation in which the results of two meta-analyses demonstrated superiority in relation to placebo and pentoxifylline, since it increases painless walking distance and functional capacity,[24] bringing benefits to quality of life.[25] In that situation, according to the guidelines of the American College of Cardiology and the American Heart Association, its recommendation degree is class I (procedure is useful and effective) and strength of scientific evidence A (based on multiple randomized studies).[26]

This drug is classified as platelet antiaggregating and anti-thrombotic agent[27] with vasodilating action,[28] and there is no evidence of prolonged bleeding time when compared with aspirin, clopidogrel or ticlopidine,[29,30] even using a combination of those (Comerota). It causes potent and selective phosphodiesterase III inhibition, causing increase in cAMP because it blocks hydrolysis in thrombocytes and smooth muscle cells, reducing intracellular calcium with consequent relaxation and vasodilation.[31] cAMP, in turn, is one of the regulators of inflammatory and immunologic reactions.[32] Cilostazol, therefore, is directly associated with the opening of high-conductance calcium-activated potassium channels (Maxi-K) via activation of kinase proteins and also TNF-α suppression and expression of adherent cells.[33]

A preclinical study demonstrated that cilostazol resulted in inhibition of thrombosis formation in the carotid artery, and that it could be useful to prevent strokes.[34] In a study of placebo-controlled cilostazol including 141 patients with type II diabetes mellitus, followed for 12 months, there was reduction in carotid intimal-medial thickness verified by high-resolution B-mode ultrasound ($p < 0.05$, even after correction for risk factors, such as hypertension, smoking and dyslipidemia), which could have beneficial effect in atherosclerosis.[35] Another study with similar design obtained a similar result in 62 patients followed for 2.6 years ($p < 0.05$). Its efficacy as antiplatelet therapy to prevent cerebral infarction has also been demonstrated.[36]

The most frequent side effects include headache, tachycardia, palpitations, loose stools and diarrhea.[37] In two studies there was need of interrupting use of cilostazol due to headache in 1.7% of patients, in relation to 1.3% in those treated with placebo, whereas suspension due to other causes was similar between groups.[38,39] In hepatic insufficiency, Child-Pugh classes B and C, prescription should be careful.[40] It is contraindicated in patients with congestive heart failure[41] or

ejection fraction of the left ventricle lower than 40%.[42]

Actions of cilostazol in central nervous system blood flow

Lee et al. demonstrated regression of cerebral lesion size induced by focal cerebral ischemia through edema reduction and improvement in neurologic deterioration in rats treated with cilostazol[43] and improvement in spatial memory learning ($p < 0.05$).[44] There was also reduction in white and gray matter cerebral lesion volume in rodents submitted to focal cerebral ischemia in 45% ($p < 0.02$) and axonal damage in 42.4% ($p < 0.002$) compared with placebo, and increase in cerebral blood flow and volume in the peri-infarction region ($p < 0.05$).[45]

This drug caused dilatation of the medial cerebral artery in pigs, even with possible nitric oxide disorder resulting from cerebral infarction and vasospasm,[46] a result that was also found in human beings, but with no increase in regional flow ($p = 0.02$).[47]

Cilostazol had dose-dependent vasodilation in penetrating cerebral arterioles in rabbits, pressurized *in vitro* independently of nitric oxide synthase antagonism by LG-nitroarginine methyl ester, and inhibition of vasodilating protaglandins by aspirin or by endothelial cell chemical denudation. The same occurred in the presence of thromboxane A^2 and 5-hydroxytryptamine, when it seems to have direct action on vessel resistance-diameter binomial to change blood flow rate, and may contribute to prevention of cerebral lacunar infarction,[48] a disease defined as a small infarction involving occlusion of penetrating arterioles.[49] In cats, it inhibits formation of platelet thrombi after medial cerebral artery occlusion and induces significant dilatation.[50]

In another study, there was suppression of astrocyte and microglial cell activation, besides increase in number of oligodendrocytes, secondary to chronic cerebral hypoperfusion, reducing cell death due to apoptosis, in association with reduced production of TNF-α, caspase-3-positive cells, TUNEL-positive cells and OX-42 ($p < 0.05$), GFAP and CNPase ($p < 0.01$), in the white matter of rats submitted to bilateral occlusion of common carotid arteries, preventing formation of vacuoles and rarefaction.[51]

Cilostazol caused reduction in BAX and cytochrome c, as well as increase in Bcl-2, ensuring survival after cerebral ischemia in rats,[52] whose ability may be associated with its capacity of maintaining the calcium rate and increasing the membrane potential of mitochondria. It showed neuroprotective effect against focal cerebral ischemia associated with antiapoptotic activity, reducing TNF-α, BAX, cytochrome c, and increasing Bcl-2 ($p < 0.001$), suppressing DNA fragmentation and cell death due to oxidative stress in animals submitted to medial cerebral artery occlusion.[53]

It reduced TNF-α level and PTEN phosphorilation, increasing Akt and CREB phosphorilation in culture of human cortical neurons (HCN 1A); in addition, it increased CK2 phosphorilation in human neuroblastoma cells (SK-N-SH), opening maxi-K channels[54] and corroborating previous findings.[55] Cilostazol also reduced PTEN phosphorilation and increased the level of CK2 ($p < 0.001$), Akt and CREB phosphorilation, in association with increase in Bcl-2 protein in the ischemia area, besides opening maxi-K channels in rats.[56] Such cilostazol activity can be due to its function in opening of calcium channels, associated with regulation of homeostase in mitochondria, which is essential for cell survival,[57] avoiding white matter apoptosis.[58] It reduced apoptosis by reducing DNA fragmentation, CREB and PTEN phosphorilation rate, causing regression in size of cerebral infarction in animals submitted to focal cerebral ischemia.[59]

The TOSS study,[60] a randomization of 135 patients with acute symptomatic stenosis of the medial or basilar cerebral artery after stroke followed by 6 months, showed progression of the atherosclerotic plaque in 6.7% in the cilostazol group vs. 28.8% in the control group ($p = 0.008$), and a plaque regression in 24.4% in the cilostazol group vs. 15.4% in the control group.

In a multicentered clinical trial including 1,052 placebo-controlled cilostazol patients, it was demonstrated that a 12-month administration was safe and effective in preventing recurrent cerebral infarction, with a 41.7% reduction in relative risk ($p = 0.015$; CI95% 9.2-62.5), especially lacunar infarction, without affecting occurrence of intracranial hemorrhage,[61] stressing the drug neuroprotective vascular activity[62] and signaling a possible beneficial cost-effectiveness ratio in pharmacoeconomic analysis, when compared to aspirin.[63] Prevention of silent cerebral infarction was reported in a study of 89 patients, placebo-controlled, and with a 3.6-year follow-up ($p < 0.001$). Mochizuki et al., using single photon emission computed tomography (SPECT),[64] demonstrated increased cerebral blood flow in a non-controlled study with a 3-month follow-up. Oishi et al. reported increased blood flow in the frontal white matter, temporal and occipital cortex in relation to ticlopidine in patients in chronic stage of cerebral infarction, also using SPECT.[65] There was also evidence of increase in cerebral flow in patients with chronic cerebral infarction after administration for 2 weeks both in the affected and non-affected side, using the method of xenon-133 inhalation.[66]

Conclusion

Use of cilostazol is well established in POAD, and may play a major role in cerebral atherosclerosis, both as vasodilator[28] and to stabilize calcium rate, increasing the membrane potential of mitochondria.[56]

Therefore, it has demonstrated its activity in microglia and astrocyte suppression and stimulation of oligodendrocytes. It also reduced cell death due to apoptosis and oxidative stress, with activity in proinflammatory cytokines, DNA fragmentation,[51] besides reducing size of ischemic lesions in experimental studies.[48]

In clinical research, cilostazol proved to be effective in increasing cerebral blood flow,[64-66] in reducing relative risk of recurrent cerebral infarction, especially lacunar, and was useful in secondary prevention.[61]

References

1. Deutsch G, Tweedy JR. Cerebral blood flow in severity-matched Alzheimer and multi-infarct patients. Neurology. 1987;37:431-8.

2. Boone KB, Miller BL, Lesser IM, et al. Neuropsychological correlates of white-matter lesions in healthy elderly subjects: a threshold effect. Arch Neurol. 1992;49:549-54.

3. Ihara M, Tomimoto H, Kinoshita M, et al. Chronic cerebral hypoperfusion induces MMP-2 but not MMP-9 expression in the microglia and vascular endothelium of white matter. J Cereb Blood Flow Metab. 2001;21:828-34.

4. Tanaka K, Ogawa N, Asanuma M, Kondo Y, Nomura M. Relationship between cholinergic

dysfunction and discrimination learning disabilities in Wistar rats following chronic cerebral hypoperfusion. Brain Res. 1996;729:55-65.

5. Wakita H, Tomimoto H, Akiguchi I, et al. Axonal damage and demyelination in the white matter after chronic cerebral hypoperfusion in the rat. Brain Res. 2002;924:63-70.

6. Wakita H, Tomimoto H, Akiguchi I, Lin JX, Miyamoto K, Oka N. A ciclooxygenase-2 inhibitor attenuates white matter damage in chronic cerebral ischemia. Neuroreport. 1999;10:1461-5.

7. Sawada M, Kondo N, Suzumura A, Marunouchi T. Production of tumor necrosis factor-alpha by microglia and astrocytes in culture. Brain Res. 1989;491:394-7.

8. Taupin V, Renno T, Bourbonniere L, Peterson AC, Rodriguez M, Owens T. Increased severity of experimental autoimmune encephalomyelitis, chronic macrophage/microglial reactivity, and demyelination in transgenic mice producing tumor necrosis factor-alpha in the central nervous system. Eur J Immunol. 1997;27:905-13.

9. Kurumatani T, Kudo T, Ikura Y, Takeda M. White matter changes in the gerbil brain under chronic cerebral hypoperfusion. Stroke. 1998;29:1058-62.

10. Petito CK, Olarte JP, Roberts B, Nowak TS Jr, Pulsinelli WA. Selective glial vulnerability following transient global ischemia in rat brain. J Neuropathol Exp Neurol. 1998;57:231-8.

11. Akiguchi I, Tomimoto H, Suenaga T, Wakita H, Budka H. Alterations in glia and axons in the brains of Binswanger's disease patients. Stroke. 1997;28:1423-9.

12. Tomimoto H, Ihara M, Wakita H, et al. Chronic cerebral hypoperfusion induces white matter lesions and loss of oligodendroglia with DNA fragmentation in the rat. Acta Neuropathol. 2003;106:527-34.

13. Hollensworth SB, Shen C, Sim JE, Spitz DR, Wilson GL, LeDoux SP. Glial cell type-specific responses to menadione-induced oxidative stress. Free Radic Biol Med. 2000;28:1161-74.

14. Pantoni L, Garcia JH, Gutierrez JA. Cerebral white matter is highly vulnerable to ischemia. Stroke. 1996;27:1641-6; discussion 1647.

15. Sgonc R, Wick G. Methods for the detection of apoptosis. Int Arch Allergy Immunol. 1994;105:327-32.

16. Borutaite V, Jekabsone A, Morkuniene R, Brown GC. Inhibition of mitochondrial permeability transition prevents mitochondrial dysfunction, cytochrome c release and apoptosis induced by heart ischemia. J Mol Cell Cardiol. 2003;35:357-66.

17. Liedtke W, Edelmann W, Bieri PL, et al. GFAP is necessary for the integrity of CNS white matter architecture and long-term maintenance of myelination. Neuron. 1996;17:607-15.

18. Narita M, Yoshida T, Nakajima M, et al. Direct evidence for spinal cord microglia in the development of a neuropathic pain-like state in mice. J Neurochem. 2006:97:1337-48.

19. Vogel US, Reynolds R, Thompson RJ, Wilkin GP. Expression of the 2',3'-cyclic nucleotide 3'-phosphohydrolase gene and immunoreactive protein in oligodendrocytes as revealed by in situ hybridization and immunofluorescence. Glia. 1988;1:184-90.

20. Datta SR, Brunet A, Greenberg ME. Cellular survival: a play in three Akts. Genes Dev. 1999;13:2905-27.

21. Allende JE, Allende CC. Protein kinase CK2: an enzyme with multiple substrates and a puzzling regulation. FASEB J. 1995;9:313-23.

22. Tamura M, Gu J, Matsumoto K, Aota S, Parsons R, Yamada KM. Inhibition of cell migration, spreading, and focal adhesions by tumor suppressor PTEN. Science. 1998;280:1614-7.

23. Walton MR, Dragunow I. Is CREB a key to neuronal survival? Trends Neurosci. 2000;23:48-53.

24. Thompson PD, Zimet R, Forbes WP, Zhang P. Meta-analysis of results from eight randomized, placebo-controlled trials on the effect of cilostazol on patients with intermittent claudication. Am J Cardiol. 2002;90:1314-9.

25. Regensteiner JG, Ware JE Jr., McCarthy WJ, et al. Effect of cilostazol on treadmill walking, community-based walking ability, and health-related quality of life in patients with intermittent claudication due to peripheral arterial disease: meta-analysis of six randomized controlled trials. J Am Geriatr Soc. 2002;50:1939-46.

26. Hirsch AT, Haskal ZJ, Hertzer NR, et al. ACC/AHA 2005 Practice Guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic): a collaborative report from the American Association for Vascular Surgery/Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society of Interventional Radiology, and the ACC/AHA Task Force on Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients With Peripheral Arterial Disease): endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation; National Heart, Lung, and Blood Institute; Society for Vascular Nursing; TransAtlantic Inter-Society Consensus; and Vascular Disease Foundation. Circulation. 2006;113:e463-654.

27. Kimura Y, Tani T, Kanbe T, Watanabe K. Effect of cilostazol on platelet aggregation and experimental thrombosis. Arzneimittelforschung. 1985;35:1144-9.

28. Yasuda K, Sakuma M, Tanabe T. Hemodynamic effect of cilostazol on increasing peripheral blood flow in arteriosclerosis obliterans. Arzneimittelforschung. 1985;35:1198-200.

29. Kim JS, Lee KS, Kim YI, Tamai Y, Nakahata R, Takami H. A randomized crossover comparative study of aspirin, cilostazol and clopidogrel in normal controls: analysis with quantitative bleeding time and platelet aggregation test. J Clin Neurosci. 2004;11:600-2.

30. Tamai Y, Takami H, Nakahata R, Ono F, Munakata A. Comparison of the effects of acetylsalicylic acid, ticlopidine and cilostazol on primary hemostasis using a quantitative bleeding time test apparatus. Haemostasis. 1999;29:269-76.

31. Shrör K. The pharmacology of cilostazol. Diabetes Obes Metab. 2002;4 Suppl 2:S14-9.

32. Katakami Y, Nakao Y, Koizumi T, Katakami N, Ogawa R, Fujita T. Regulation of tumour necrosis factor production by mouse peritoneal macrophages: the role of cellular cyclic AMP. Immunology. 1988;64:719-24.

33. Park SY, Lee JH, Kim CD, et al. Cilostazol suppressed superoxide production and expression of adhesion molecules in human endothelial cells via mediation of cAMP-dependent protein kinase-mediated Maxi-K channel activation. J Pharmacol Exp Ther. 2006;317:1238-45.

34. Kohda N, Tani T, Nakayama S, et al. Effect of cilostazol, a phosphodiesterase III inhibitor, on experimental thrombosis in the porcine carotid artery. Thromb Res. 1999;96:261-8.

35. Ahn CW, Lee HC, Park SW, et al. Decrease in carotid intima media thickness after 1 year of cilostazol treatment in patients with type 2 diabetes mellitus. Diabetes Res Clin Pract. 2001;52:45-53.

36. Caplan LR. Antiplatelet therapy in stroke prevention: present and future. Cerebrovasc Dis. 2006;21 Suppl 1:1-6.

37. Sorkin EM, Markham A. Cilostazol. Drugs Aging. 1999;14:63-71.

38. Beebe HG, Dawson DL, Cutler BS, et al. A new pharmacological treatment for intermittent claudication: results of a randomized, multicenter trial. Arch Intern Med. 1999;159:2041-50.

39. Money SR, Herd JA, Isaacsohn JL, et al. Effect of cilostazol on walking distances in patients with intermittent claudication caused by peripheral vascular disease. J Vasc Surg. 1998;27:267-74.

40. Bramer SL, Forbes WP. Effect of hepatic impairment on the pharmacokinetics of a single dose of cilostazol. Clin Pharmacokinet. 1999;37 Suppl 2:25-32.

41. Regensteiner JG, Hiatt WR. Current medical therapies for patients with peripheral arterial disease: a critical review. Am J Med. 2002;112:49-57.

42. Mukherjee D, Yadav JS. Update on peripheral vascular diseases: from smoking cessation to stenting. Cleve Clin J Med. 2001;68:723-33.

43. Lee JH, Lee YK, Ishikawa M, et al. Cilostazol reduces brain lesion induced by focal cerebral ischemia in rats – an MRI study. Brain Res. 2003;994:91-8.

44. Watanabe T, Zhang N, Liu M, Tanaka R, Mizuno Y, Urabe T. Cilostazol protects against brain white matter damage and cognitive impairment in a rat model of chronic cerebral hypoperfusion. Stroke. 2006;37:1539-45.

45. Honda F, Imai H, Ishikawa M, et al. Cilostazol attenuates gray and white matter damage in a rodent model of focal cerebral ischemia. Stroke. 2006;37:223-8.

46. Birk S, Kruuse C, Petersen KA, Jonassen O, Tfelt-Hansen P, Olesen J. The phosphodiesterase 3 inhibitor cilostazol dilates large cerebral arteries in humans without affecting regional cerebral blood flow. J Cereb Blood Flow Metab. 2004;24:1352-8.

47. Birk S, Edvinsson L, Olesen J, Kruuse C. Analysis of the effects of phosphodiesterase type 3 and 4 inhibitors in cerebral arteries. Eur J Pharmacol. 2004;489:93-100.

48. Nakamura K Ikomi F, Ohhashi T. Cilostazol, an inhibitor of type 3 phosphodiesterase, produces endothelium-independent vasodilation in pressurized rabbit cerebral penetrating arterioles. J Vasc Res. 2006;43:86-94.

49. Bamford J, Sandercock P, Dennis M, Burn J, Warlow C. Classification and natural history of clinically identifiable subtypes of cerebral infarction. Lancet. 1991;337:1521-6.

50. Tanaka K, Gotoh F, Fukuuchi Y, et al. Effects of a selective inhibitor of cyclic AMP phosphodiesterase on the pial microcirculation in feline cerebral ischemia. Stroke. 1989;20:668-73.

51. Lee JH, Park SY, Shin YW, et al. Neuroprotection by cilostazol, a phosphodiesterase type 3 inhibitor, against apoptotic white matter changes in rat after chronic cerebral hypoperfusion. Brain Res. 2006;1082:182-91.

52. Chen J, Graham SH, Nakayama M, et al. Apoptosis repressor genes Bcl-2 and Bcl-x-long are expressed in the rat brain following global ischemia. J Cereb Blood Flow Metab. 1997;17:2-10.

53. Choi JM, Shin HK, Kim KY, Lee JH, Hong KW. Neuroprotective effect of cilostazol against focal cerebral ischemia via antiapoptotic action in rats. J Pharmacol Exp Ther. 2002;300:787-93.

54. Hong KW, Lee JH, Kima KY, Park SY, Lee WS. Cilostazol: therapeutic potential against focal cerebral ischemic damage. Curr Pharm Des. 2006;12:565-73.

55. Hong KW, Kim KY, Shin HK, et al. Cilostazol prevents tumor necrosis factor-α-induced cell death by suppression of phosphatase and tensin homolog deleted from chromosome 10 phosphorylation and activation of akt/cyclic AMP response element-binding protein phosphorylation. J Pharmacol Exp Ther. 2003;306:1182-90.

56. Lee JH, Kim KY, Lee Y, et al. Cilostazol prevents focal cerebral ischemic injury by enhancing casein kinase 2 phosphorylation and suppression of phosphatase and tensin homolog deleted from chromosome 10 phosphorylation in rats. J Pharmacol Exp Ther. 2004;308:896-903.

57. Wu S, Liu S, Huang M. Cilostazol, an inhibitor of type 3 phosphodiesterase, stimulates large-conductance, calcium-activated potassium channels in pituitary GH^3 cells and pheochromocytoma PC12 cells. Endocrinology. 2004;145:1175-84.

58. Zhu L, Ling S, Yu XD, et al. Modulation of mitochondrial Ca2 homeostasis by Bcl-2. J Biol Chem. 1999;274:33267-73.

59. Lee JH, Park SY, Lee WS, Hong KW. Lack of antiapoptotic effects of antiplatelet drug, aspirin and clopidogrel, and antioxidant, MCI-186, against focal ischemic brain damage in rats. Neurol Res. 2005;27:483-92.

60. Kwon SU, Cho YJ, Koo JS, et al. Cilostazol prevents the progression of the symptomatic intracranial arterial stenosis: the multicenter double-blind placebo-controlled trial of cilostazol in symptomatic intracranial arterial stenosis. Stroke. 2005;36:782-6.

61. Gotoh F, Tohgi H, Hirai S, et al. Cilostazol stroke prevention study: a placebo-controlled double-blind trial for secondary prevention of cerebral infarction. J Stroke Cerebrovasc Dis. 2000;9:147-57.

62. Matsumoto M. Cilostazol in secondary prevention of stroke: impact of the Cilostazol Stroke Prevention Study. Atheroscler Suppl. 2005;6:33-40.

63. Inoue T, Kobayashi M, Uetsuka Y, Uchiyama S. Pharmacoeconomic analysis of cilostazol for the secondary prevention of cerebral infarction. Circ J. 2006;70:453-8.

64. Mochizuki Y, Oishi M, Mizutani T. Effects of cilostazol on cerebral blood flow, P300, and serum lipid levels in the chronic stage of cerebral infarction. J Stroke Cerebrovasc Dis. 2001;10:63-9.

65. Oishi M, Mochizuki Y, Shikata E, Satoh Y. Effect of cilostazol on cerebral blood flows in chronic stage of cerebral circulation. Keio J Med. 2000;49 Suppl 1:A145-7.

66. Kobayashi S, Yamaguchi S, Katsube T, Kitani M, Okada K, Tsunematsu Y. Long-term effect of cilostazol on cerebral blood flow in chronic cerebral infarction. Arzneimittelforschung. 1985;35:1193-7.

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