REVIEW ARTICLE

The pharmacology of cilostazol

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Cilostazol (6-[4-(1-cyclohexyl-*1H*-tetrazol-5-yl)butoxy]-3,4-dihydro-2(1*H*)-quinolinone; OPC-13013) is a 2-oxo-quinoline derivative with antithrombotic, vasodilator, antimitogenic and cardiotonic properties. The compound is a potent inhibitor of phosphodiesterase (PDE) 3A, the isoform of PDE 3 in the cardiovascular system (IC_{50}: 0.2 μM). In addition, there is inhibition of adenosine uptake, eventually resulting in changes in cAMP levels, dependent on the type of adenosine receptors (A_1 or A_2). Cilostazol inhibits platelet aggregation and has considerable antithrombotic effects *in vivo*. The compound relaxes vascular smooth muscle and inhibits mitogenesis and migration of vascular smooth muscle cells. In the heart, cilostazol causes positive inotropic and chronotropic effects. Most, if not all, of these actions are cAMP-mediated, including the modification of cAMP-controlled gene expression. Cilostazol decreases levels of serum triglycerides and causes some increase in HDL-cholesterol levels. The compound has a number of additional effects which might contribute to its overall clinical efficacy. Cilostazol undergoes intensive and finally complete hepatic metabolism via the cytochrome P450 systems. This might result in some drug interaction, i.e. with erythromycin and omeprazole. The half-life is approximately 10 h, resulting in about 2-fold accumulation of the drug during repeated administration.

Key words: peripheral arterial disease, cilostazol, pharmacology

Introduction

Cilostazol (6-[4-(1-cyclohexyl-*1H*-tetrazol-5-yl)butoxy]-3,4-dihydro-2(1*H*)-quinolinone; OPC-13013) (Fig. 1) is an antiplatelet vasodilator agent that has been used for more than a decade in Japan for the treatment of chronic peripheral arterial occlusive disease. Cilostazol is also approved for this indication by the US Food and Drug Administration. This article reviews some basic pharmacological actions of cilostazol that might be relevant for its clinical efficacy.

Mode of action of cilostazol

Cilostazol is a selective and potent inhibitor of phosphodiesterase (PDE) 3A (IC_{50}: 0.2 μM), the cardiovascular subtype of PDE 3. At therapeutic plasma levels of about 3–5 μM [1], the compound does not affect other PDEs; however, the local tissue levels of the compound might be higher than the free concentration in plasma because of the lipophilicity of the drug. Importantly, there is no relevant effect by cilostazol on PDE 1, 2 and 4 at comparable concentrations, and only a minor effect on PDE 5 (IC_{50}: 5–8 μM). PDE 3 increases the breakdown of cAMP. Since both platelets and vascular smooth muscle cells contain PDE 3A, this mechanism appears to explain the inhibition of platelet function as well as the vasodilatory effects [2].

More recently, another pharmacological property of cilostazol has been detected: inhibition of adenosine uptake. This leads to enhanced adenosine actions via A_1 and A_2-receptors. In platelets and vascular cells, A_2-mediated increases in cAMP enhance the consequences of PDE-inhibition, i.e. result in additional increases in cAMP. In cardiocytes, carrying the A_1-receptor subtype, there will be a G_i-mediated inhibition of adenylate cyclase with subsequent reduction in cAMP (Fig. 2). Whether this concept works *in vivo*,

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is currently unknown. According to current knowledge, the actions of cilostazol that are most important for its clinical efficacy involve effects on platelets and vascular cells.

Antiplatelet and antithrombotic effects

Cilostazol inhibits platelet aggregation, an effect which is potentiated by prostaglandin E_1 and probably mediated *in vitro* via PDE 3 inhibition and subsequent cAMP accumulation [3] (Fig. 3). Interestingly, cilostazol is also active in shear-stress induced platelet aggregation, whereas aspirin is not. Moreover, cilostazol appears not to prolong bleeding time [4] and bleeding is also not a significant side-effect [5]. This is in clear contrast to the conventional antiplatelet agents aspirin and ticlopidine [5] and suggests a different mode of action.

The antiplatelet actions of cilostazol might be enhanced by inhibition of adenosine uptake. Liu and colleagues [6] have shown that cilostazol enhances the interstitial concentration of adenosine in several *in vitro* and *in vivo* models. In platelets this will result in stimulation of A_2 receptors and further increase in levels of cAMP (Fig. 2).

In vivo, cilostazol is an effective antithrombotic agent. It has also been reported to be more effective than ticlopidine in the prevention of carotid thrombosis after endothelial injury [7].

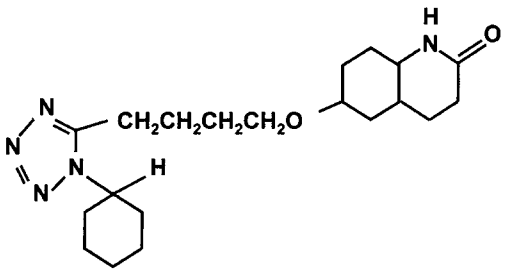

Fig. 1 Chemical structure of cilostazol.

Vascular cells

Cilostazol relaxes vascular smooth muscle and causes vasodilatation. Both, PDE-inhibition and possibly inhibition of adenosine uptake, may act in concert. Interestingly, cilostazol also inhibits the cytokine-induced expression of monocyte chemoattractant protein-1 (MCP-1) [8]. MCP-1 plays a significant role in mediating monocyte recruitment in atherosclerotic lesions. This effect is also probably due to cAMP elevation and might contribute to an anti-inflammatory

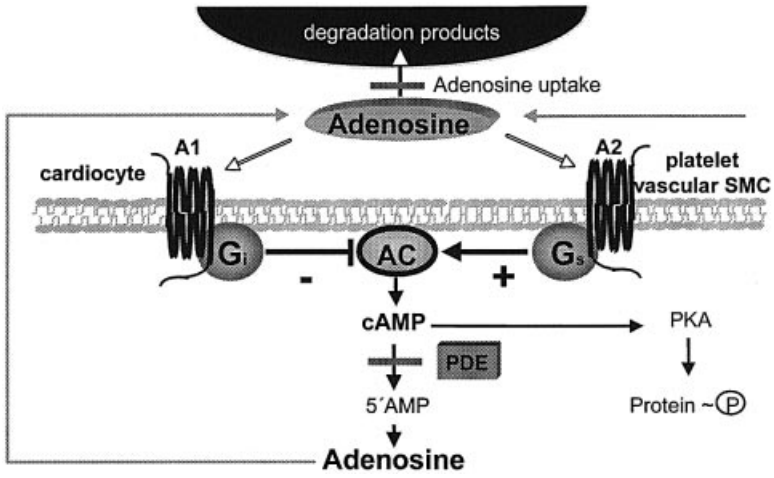

Fig. 2 Hypothetical scheme for the mode of action of cilostazol.The level of cAMP determines cAMP-mediated effects, for example, activation of second messenger induced kinases such as protein kinase A (PKA). Cyclic AMP levels are controlled by degradation via several phosphodiesterases (PDE) and biosynthesis via adenylate cyclase (AC). AC-activity in turn is controlled by stimulatory (G_s) and inhibitory (G_i) G-proteins. Adenosine, either from cellular metabolism or extracellular sources, activates G_s via A_2-receptors and G_i via A_1-receptors. This results in either amplification or inhibition of AC.

action of the compound. A recent study in patients with noninsulin-dependent diabetes mellitus has shown that oral treatment with cilostazol for 4 weeks significantly reduced the concentration of soluble adhesion molecules in the blood, probably indicating a vasoprotective action [9]. In addition, there was a reduction in serum-triglyceride levels by cilostazol in patients with intermittent claudication together with an increase in treadmill walking time [5]. All these data suggest an improved clinical situation for patients after treatment with cilostazol.

Antimitogenic effects

In addition to inhibiting platelet aggregation, cilostazol also blocks the surface expression of the platelet fibrinogen receptor (GPIIb/IIIa), as well as alpha-granule secretion of P-selectin [1]. P-selectin is assumed to be involved in platelet-dependent mitogenesis. This effect might contribute to inhibition of restenosis. However, other activities of cilostazol might also be involved. This includes inhibition of heparin-binding epidermal growth factor-like growth factor (HB-EGF) in macrophages and vascular smooth muscle cells [10]. HB-EGF is one of the most potent mitogens for vascular smooth muscle cells and inhibition of its expression is clearly of relevance for inhibition of mitogenesis. Thus, cilostazol might act as an antimitogenic agent by several mechanisms: increase in cAMP and interference with the cell cycle, and direct interference with several growth factors.

In the rat carotid injury model, single local application of cilostazol resulted in a marked inhibition of intima proliferation. Interestingly, the tissue concentration of cilostazol in the carotid artery and muscle around the carotid artery was considerably higher than in plasma [11]. This is suggestive of a significant tissue accumulation of the compound, probably related to its highly lipophilic nature. There was also suppression of neointimal formation in dog grafted veins, which, interestingly, appeared to be related to inhibition of angiotensin II forming enzymes [12]. Significant inhibition of intimal proliferation after directional coronary atherectomy was also obtained in humans [13].

Heart

Actions on the heart of PDE 3 inhibitory agents are most relevant in terms of side-effects. PDE 3 inhibitors elevate the cAMP content in cardiocytes, eventually resulting in inotropic and chronotropic effects, but possibly also in arrhythmias. Fatal arrhythmias have been described with the use of milrinone, another inhibitor of PDE 3, whereas no such side-effects are known for cilostazol. A possible explanation for this different pharmacological profile might be the inhibition of adenosine uptake by cilostazol, but not milrinone, in the heart (Fig. 4). *In vitro*, cilostazol inhibited adenosine uptake into cardiac myocytes, coronary artery smooth muscle cells and endothelial cells, with a median effective concentration of 10 μM, whereas milrinone was ineffective [14]. This might result from stimulation of adenosine A_1-receptors and might counteract the increase of cAMP via PDE-inhibition (Fig. 2).

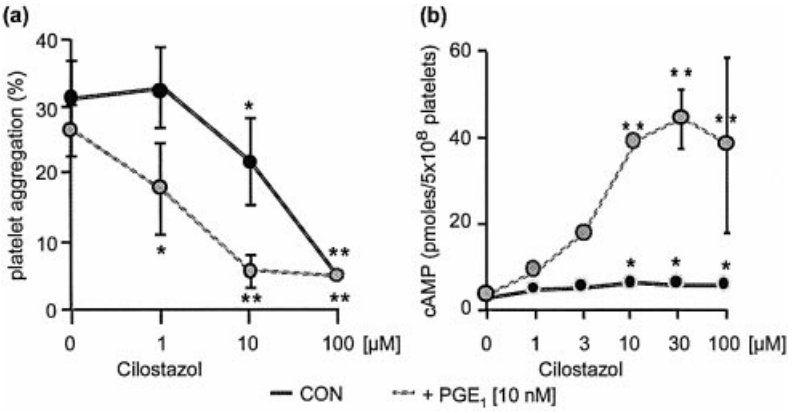

Fig. 3 Inhibition of shear stress-induced human platelet aggregation by cilostazol and potentiation of this response by PGE_1 (a). The right panel (b) demonstrates the potentiation of increase in cAMP by the combined use of these compounds. Reprinted from *Life Sciences* 61, Minami *et al.* pp PL383–389 © 1997 with permission from Elsevier Science.

Lipid-modulating effects

Cilostazol reduced plasma triglycerides and raised plasma HDL-cholesterol (Table 1). In a placebo-controlled clinical trial, the effects of treatment with cilostazol 100 mg b.d. for 12 weeks on plasma lipids was evaluated [5]. At baseline and at the end of treatment, LDL-cholesterol, HDL-cholesterol, total cholesterol, triglyceride levels, apo A-1 and apo B were determined. All study participants discontinued lipid-lowering therapy at least 4 weeks before screening, with the exception of probucol, which was to be discontinued 6 months before screening. Patients were instructed to maintain stable dietary patterns during the 12-week study period.

After 12 weeks, as compared with placebo, cilostazol 100 mg b.d. produced a clinically significant reduction in triglycerides of 0.37 mmol/L (15%) and an increase in HDL-cholesterol of 0.11 mmol/L (10%). Total cholesterol and LDL-cholesterol levels were not significantly changed from baseline in either group at the end of treatment. Similar results were seen in other controlled phase III trials.

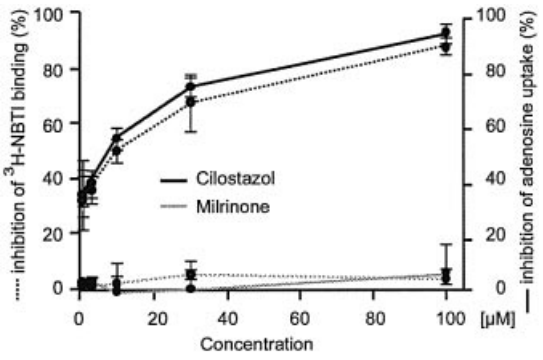

Fig. 4 Concentration-dependent inhibition of NBTI binding and adenosine uptake by cilostazol but not by milrinone [6].

Pharmacokinetics

The pharmacokinetics of cilostazol are the same in patients with intermittent claudication as in normal healthy volunteers. The pharmacokinetics at steady state of cilostazol and its metabolites 3,4-dehydro-cilostazol (OPC-13015) and 4′-*trans*-hydroxy-cilostazol (OPC-13213) following administration of cilostazol 100 mg b.d. are shown in Table 2 [15]. The half-life is approximately 10 h, resulting in about 2-fold accumulation of the drug during repeated administration [15].

The pharmacokinetics of cilostazol and its metabolites are not significantly affected by age or gender in healthy subjects aged 50–80 years [15].

There was no displacement interaction between cilostazol and its metabolites in an *in vitro* displacement study [16]. Another study reported that there was minimal *in vitro* displacement of cilostazol by omeprazole and it was not considered clinically relevant, and displacement of protein bound cilostazol did not occur with either erythromycin or quinidine [17], caution should be taken as significant increases in dehydro-cilastazol, a potent metabolite may occur with coadministration of omeprazole.

There have been no reports of clinically significant drug interactions between cilostazol and aspirin [18] or beraprost [19]. Cilostazol and its metabolites have not been reported to have a significant effect on warfarin plasma protein binding, and vice versa [16,20] nor to affect prothrombin time, activated partial thromboplastin time or Ivy bleeding times [21,22].

Sixteen healthy nonsmoking male volunteers received a single oral dose of cilostazol 100 mg with and without pretreatment with and continued administration of a cytochrome P450 CYP3A4 inhibitor, erythromcyin 500 mg three times daily [23]. Coadministration with erythromycin significantly increased cilostazol C_{max} and AUC by 47% and 74%, respectively, while producing an

Table 1 Significant effects of cilostazol on plasma lipids (mean ± SEM) [5]

	Cilostazol 100 mg b.d. (*n* = 95)		**Placebo (*n* = 94)**		
Parameter	**Baseline**	**Week 12**	**Baseline**	**Week 12**	***P*-value**
HDL-cholesterol (mmol/l)	1.09 (0.03)	1.20 (0.03)	1.14 (0.03)	1.14 (0.03)	< 0.001
Triglycerides (mmol/l)	1.84 (0.08)	1.47 (0.07)	1.85 (0.09)	1.88 (0.11)	< 0.001
Apo A-1 (mg/dL)	128 (3)	136 (3)	135 (3)	137 (3)	< 0.05
Apo B (mg/dL)	119 (2)	116 (2)	124 (2)	126 (2)	< 0.01

*Significance of differences in week 12 vs. baseline plasma lipoproteins between groups was tested by Wilcoxon's rank sum test on change from baseline

approximate 50% reduction in unbound cilostazol clearance, suggesting that CYP3A4 was the most important hepatic metabolizing enzyme involved with cilostazol metabolism.

In patients with severe renal impairment [creatinine clearance 0.3–1.6 L/h (5–25 mL/min)], cilostazol 50 mg administered daily on days 1 and 8, and twice daily on days 2–7, produced C_{max} and $AUC_{0-12\ h}$-values that were 29% and 39% lower, respectively, than in healthy volunteers (P = ns). Both the free fraction of cilostazol and unbound cilostazol clearance were significantly higher (27% and 58% increases, respectively) in the group with severe renal disease [24].

The pharmacokinetic profile of single dose cilostazol (100 mg) was investigated in 12 patients with impaired liver function (10 mild, 2 moderate) and 12 healthy volunteers. There was no difference in protein binding between those with hepatic impairment and healthy individuals (94.6% vs. 95.2%), but patients with hepatic dysfunction had reduced oral cilostazol clearance and total urinary metabolites compared with controls. Overall, however, the pharmacokinetics of cilostazol and its monohydroxy and dehydroxy metabolites were not substantially different in patients with mild to moderate hepatic disease from those measured in healthy individuals [25].

Conclusion

Cilostazol has a broad spectrum of pharmacological effects that may work together to improve blood flow in the lower extremities. The principal pharmacological effects of cilostazol are antiplatelet/antithrombotic activity, vasodilatation and improvement in plasma lipids.

Table 2 Steady-state pharmacokinetic parameters following administration of cilostazol 100 mg b.d. in patients with intermittent claudication [15]

Analyte	t_{max} (h)	C_{max} (ng/mL)	AUC 0–12 h (ng/h/mL)	$t_{1/2z}$ (h)
Cilostazol	2.7 ± 1.4	1332 ± 564	10732 ± 5019	10.5 ± 4.4
	n = 26	n = 26	n = 26	n = 15
OPC-13015	5.2 ± 9.0	426 ± 158	4148 ± 1712	11.7 ± 3.8
	n = 25	n = 26	n = 26	n = 19
OPC-13213	3.0 ± 1.8	224 ± 89	1956 ± 810	13.3 ± 4.8
	n = 26	n = 26	n = 26	n = 16

t_{max}, time to maximum plasma concentration; C_{max}, maximum plasma concentration; AUC, area under the curve; $t_{1/2z}$, terminal elimination half-life

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