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Forum Minireview

Novel Situations of Endothelial Injury in Stroke — Mechanisms of Stroke and Strategy of Drug Development: Protective Effects of Antiplatelet Agents Against Stroke

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Abstract. Stroke is the second cause of mortality worldwide, and intravenous administration of tissue plasminogen activator (t-PA) within 3 h of symptom onset is the only treatment proven effective for re-establishment of cerebral blood flow following acute ischemic stroke. However, its widespread application remains limited by its narrow therapeutic time window and the related risks of intracranial hemorrhage. On the other hand, in patients with atherothrombotic risk, antiplatelet agents are widely used to decrease the risk of occlusive arterial events. All of these drugs are used during coronary interventions and in the medical management of acute coronary syndromes. In contrast, only aspirin, cilostazol, and thienopyridine derivatives (ticlopidine and clopidogrel) are used in the long-term prevention of cerebrovascular events in patients with risk of recurrence. In this paper, we introduce recent clinical findings on antiplatelet therapies for secondary prevention after ischemic stroke and describe basic research that has focused on cerebrovascular protection by cilostazol, which has a unique pharmacological profile.

Keywords: antiplatelet therapy, cerebrovascular protection, cilostazol, intracerebral hemorrhage, stroke, endothelial injury

1. Introduction

Stroke is the second cause of mortality worldwide and it is the most common cause of neurological disability in older individuals (1). Intravenous administration of tissue plasminogen activator (t-PA) within 3 h of symptom onset is the only treatment proved effective for re-establishment of cerebral blood flow in acute ischemic stroke. The clinical efficacy of treatment with recombinant tissue plasminogen activator (rt-PA) within a few hours after the onset of the ischemic attack has also been demonstrated by the National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group (2). However, if there is a delay in administration of rt-PA or in reperfusion, hemorrhagic transformation can occur, often with fatal results. Therefore, reduction in tPA-associated blood–brain barrier (BBB) injury by any means may extend the time window for safe and effective reperfusion therapy. One of the factors that causes hemorrhagic transformation may be a disruption of the BBB, which consists primarily of endothelium (3). For this reason, the proper treatment for acute brain ischemia might include not only thrombolytic therapy, but also BBB protection.

A previous study has shown that the cumulative risk for recurrent stroke and death is higher in the first year, with an 8% risk for recurrent stroke and a 24.5% risk for death; however, the rates continued to increase with an 18.1% risk for recurrent stroke and a 41.3% risk for death within 4 years (4). In patients with atherothrombotic risk, antiplatelet therapies with aspirin, dipyridamole, thienopyridine derivatives (clopidogrel and ticlopidine), or cilostazol (Fig. 1) are widely used to decrease the risk of occlusive arterial events and meta-analyses have demonstrated the efficacy of antiplatelet therapies for secondary prevention after ischemic stroke. In this paper, we introduce recent clinical findings on antiplatelet therapies for secondary prevention after ischemic stroke and

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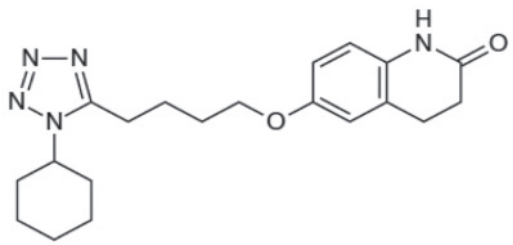

Fig. 1. Chemical structure of 6-[4-(1-cyclohexyl-1*H*-tetrazol-5-yl) butoxy]-3,4-dihydro-2(1*H*)-quinolinone (cilostazol).

report on basic research that has focused on the cerebrovascular protective properties of cilostazol, which has a unique pharmacological profile.

2. Antiplatelet therapies for secondary prevention after ischemic stroke (Table 1)

Platelet activation, adhesion, and aggregation play a pivotal role in the pathogenesis of arterothrombosis. Aspirin is the first line of antiplatelet agents, although its efficacy is modest, with 13% reduction (95% CI, 4% – 21%) (5). The low efficacy is thought to be a consequence of aspirin resistance (6); that is, the inability of aspirin to reduce platelet production of thromboxane A_2 and thereby platelet activation and aggregation. The overall effect of aspirin is attributed to its ability to inhibit platelet cyclooxygenase (COX), thus preventing the formation of thromboxane A_2, a potent platelet activator and vasoconstrictor. However, platelets contain, in addition to COX-1, variable amounts of COX-2 (7), which is at least two orders of magnitude less sensitive to inhibition by aspirin than COX-1 (8). An insufficient platelet response to aspirin has therefore been surmised to be caused by thromboxane formation via platelet COX-2. Aspirin also inhibits the synthesis of prostaglandin I_2 in the endothelium — an undesirable situation, as this prostanoid seems to have potent antiplatelet and vasodilator effects (9) Aspirin can also induce gastrointestinal irritation and bleeding by a mechanism that may involve both inhibition of prostaglandin synthesis and direct damage to the gastric and intestinal mucosa through contact with ingested aspirin-containing tablets (10, 11). These factors may explain why aspirin is neither fully effective nor entirely clinically acceptable.

The activation pathways of other agonists, such as ADP, 5-HT, and thrombin, among others, are not inhibited by aspirin (9); therefore, a wide variety of antiplatelet agents such as thienopyridine derivatives (clopidogrel and ticlopidine), dipyridamole, or cilostazol is used for secondary prevention after ischemic stroke. Thienopyridines (ticlopidine and clopidogrel) decrease platelet aggregation by inhibiting the binding of adenosine 5′-diphosphate (ADP) to platelet $P2Y_{12}$ receptor (12). Ticlopidine has shown a significant 23.3% relative risk reduction in the combined end point of stroke, myocardial infarction, or vascular death compared with a placebo group (11.3% per year vs. 14.8% per year; $P = 0.02$) in the Canadian American Ticlopidine Study (CATS) (13) and a significant 12% relative risk reduction in the primary end point of nonfatal stroke or death compared with those receiving aspirin (17% vs. 19%, $P = 0.048$) in the Ticlopidine Aspirin Stroke Study (TASS) (14). In the Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial (15), clopidogrel was associated with a significant 8.7% relative risk reduction (95% CI, 0.3% – 16.5%) compared with aspirin for the primary end point of ischemic stroke, myocardial infarction, or vascular death (5.32% vs. 5.83% per year; $P = 0.043$). However, the benefit of clopidogrel was not statistically significant for the 6,431 patients in the stroke subgroup (7.15% vs. 7.71% per year, $P = 0.26$).

Table 1. Antiplatelet therapies for secondary prevention after ischemic stroke

Comparison(s)	Study name	N	Study duration	Relative risk reduction for stroke events	Ref. No.
Aspiron vs. control	10 randomized trials	6,171	17 – 50 months	13% reduction (95% CI, 4% – 21%)	5
Ticlopidine vs. control	CATS	1,053	2 years	23.3% reduction (11.3% vs. 14.8%, $P = 0.02$)	13
Ticlopidine vs. aspirin	TASS	3,069	3 years	12% reduction (17% vs. 19%, $P = 0.048$)	14
Clopidogrel vs. aspirin	CAPRIE	6,431	1.91 years	7.3% reduction (7.15% vs. 7.71%, $P = 0.26$)	15
Dipyridamole vs. control	ESPS-2	3,303	2 years	16.3% reduction (12.8% vs. 15.2%, $P = 0.039$)	16
Dipyridamole + aspirin vs. aspirin	ESPS-2	3,299	2 years	23.1% reduction (9.5% vs. 12.5%, $P = 0.006$)	16
Dipyridamole + aspirin vs. aspirin	ESPRIT	2,739	3.5 years	22% reduction (10.9% vs. 14.0%)	22
Cilostazol vs. control	CSPS	1,034	21.4 months	40.3% reduction (3.43% vs. 5.75%, $P = 0.0205$)	20
Cilostazol vs. aspirin	CSPS-2	2,672	29 months	25.7% reduction (2.76% vs. 3.71%, $P = 0.0357$)	21

Dipyridamole is a nonspecific phosphodiesterase (PDE) inhibitor that inhibits degradation of cyclic AMP and/or cyclic GMP, and it inhibits platelet aggregation and vasoconstriction. In the European Stroke Prevention Study 2 (ESPS-2) (16), extended-release dipyridamole (ER-DP) significantly reduced the recurrent incidence of stroke compared with placebo [aspirin vs. placebo: 12.5% vs. 15.2%, relative-risk reduction (RRR) 18.1%, $P = 0.013$; ER-DP vs. placebo: 12.8% vs. 15.2%, RRR 16.3%, $P = 0.039$].

Cilostazol increases the cyclic AMP levels in platelets via a selective inhibition of cyclic AMP-dependent PDE3 (17), and it inhibits platelet aggregation induced by a wide variety of platelet stimuli such as collagen, thrombin, ADP and so on (18, 19). In the Cilostazol Stroke Prevention Study (CSPS) (20), cilostazol treatment results in a significant 40.3% relative-risk reduction compared with the placebo with respect to the recurrence of cerebral infarction (3.43% vs. 5.75% per year, $P = 0.0205$). More recently, cilostazol showed a significant 25.7% relative risk reduction compared with aspirin in the primary endpoint of the first occurrence of stroke (2.76% vs. 3.71% per year, $P = 0.0357$) in the second Cilostazol Stroke Prevention Study (CSPS-2) (21).

Because multiple pharmacologic mechanisms are available for platelet inhibition, combinations of antiplatelet agents have the potential for synergistic effects. Indeed, the combination of aspirin and ER-DP is supported from two large studies demonstrating superiority over aspirin alone for recurrent stroke prevention in the ESPS-2 (16) and in the European/Australian Stroke Prevention in Reversible Ischemia Trial (ESPRIT) (22). Furthermore, combination therapy with clopidogrel and aspirin is more effective than aspirin alone in reducing microembolic signals in patients with predominantly intracranial symptomatic stenosis (23). In patients treated with thienopyridine plus aspirin, platelet reactivity index significantly decreased after dual antiplatelet treatment in comparison with the same patients on aspirin monotherapy, but insufficient antiplatelet response was observed in 28% of the patients (24). Therefore, combinations of antithrombotic agents do not necessarily improve clinical efficacy and are typically associated with increased intracerebral hemorrhages (ICHs).

3. ICHs during antiplatelet therapies

In the USA, the yearly estimate of ICH is 0.15% in the general population aged approximately 70 years. In general, aspirin is associated with an increase in the hemorrhagic risk of two-fold (0.3% per year) in patients with cerebrovascular diseases compared with the general population (25) and a 1.84-fold increased risk of hemorrhagic stroke (95% CI, 1.24% – 2.74%; $P = 0.001$) compared with placebo in a stroke subtype in 16 randomized controlled trials (26). As above-mentioned, thienopyridine derivatives (ticlopidine and clopidogrel), combinations of aspirin and ER-DP, or cilostazol are marginally more effective than aspirin alone in secondary prevention following ischemic stroke and do not increase the hemorrhagic complications of aspirin treatment. The occurrence of major hemorrhage associated with clopidogrel observed in the CAPRIE trial (1.4%) was similar to that seen for aspirin (1.6%) (15). Similarly, ER-DP plus aspirin resulted in rates of bleeding of any type that were similar to those of aspirin alone (8.7% vs. 8.2%) (16). Ticlopidine was found to have a lower rate of major hemorrhage (0.5%) compared to aspirin (1.4%) ($P < 0.05$), and the rates of minor bleeding were similar between the two groups (9% vs. 10%) in the TASS (14). Interestingly, hemorrhagic events in the CSPS2 occurred in fewer patients on cilostazol (0.77%) than on aspirin (1.78%, $P = 0.0004$) in patients with noncardioembolic ischemic stroke (20). In the CSPS (20), the number of ICHs during cilostazol treatment (0.78%) was not statistically different from that of the placebo (1.16%) for the 1,034 patients with noncardioembolic ischemic stroke. These findings strongly suggest that cilostazol is a potential therapeutic drug for secondary prevention after ischemic stroke without increased risk of ICHs.

Dual antiplatelet therapy such as ER-DP plus aspirin may also be a potent antiplatelet strategy in the second prevention for stroke. However, combination therapy with clopidogrel and aspirin does not appear to offer any clear advantages over either drug alone and remains associated with an increased risk of bleeding complications, as shown by the Management of Atherothrombosis with Clopidogrel in High-risk Patients (MATCH) (27) and the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trials (28). A combination study with cilostazol and aspirin, compared with aspirin alone, is now ongoing against recurrent stroke in patients with intracranial artery stenosis, in the Cilostazol-Aspirin Therapy Against Recurrent Stroke With Intracranial Artery Stenosis (CATHARSIS) trial.

4. Possible mechanisms of the protective effects of cilostazol on cerebral infarction

Cilostazol, an antiplatelet drug, increases the intracellular level of cyclic AMP by inhibiting its hydrolysis by PDE3. Unlike other antiplatelet agents, such as aspirin and thienopyridine derivatives, cilostazol has been shown to inhibit platelet aggregation induced by a variety of stimuli, including arachidonic acid, ADP, epinephrine,

collagen, thrombin, and high shear stress (19, 29, 30). Because of its unique mechanisms of action, a wide variety of pharmacological actions has been reported, including antithrombosis in feline cerebral ischemia (31), increased cerebral blood flow (32), and vasodilation via an increased cyclic AMP level (31). Interestingly, Lee et al. (33) reported that, in rat brains subjected to middle cerebral artery (MCA) occlusion followed by 24-h reperfusion, the cerebral infarct size was little affected by oral administration of aspirin (300 mg/kg) or clopidogrel (30 mg/kg), but it was significantly reduced by cilostazol (30 mg/kg). Thus, cilostazol has been suggested to have a neuroprotective effect against ischemic brain injury (34, 35). Its neuroprotective potential has been based on the following: a) its anti-inflammatory and antiapoptotic effects (mediated by scavenging of hydroxyl radicals), b) decreased formation of tumor necrosis factor-α, and c) an inhibition of poly(ADP-ribose) polymerase activity (36 – 38). We further reported that cilostazol may exert its neuroprotective effects at least in part by inducing metallothionein-1 and -2 in brain areas made ischemic by permanent MCA occlusion (39).

As mentioned in the previous section, a characteristic feature of cilostazol is that it has weaker hemorrhagic side effects than the other antiplatelet drugs; indeed, it does not increase the bleeding time (40). Previously, we found that cilostazol significantly reduced the extent of Evans blue extravasation and subsequent hemorrhagic transformation (Fig. 2) in mouse brains subjected to focal MCA occlusion and reperfusion, which supports the idea that cilostazol limits or prevents BBB disruption after ischemia/reperfusion injury (41). In addition, increasing evidence indicates that cilostazol may offer endothelial protection via both an inhibition of lipopolysaccharide-induced apoptosis (42) and an inhibition of neutrophil adhesion to endothelial cells (through down-regulation of the expression of adhesion molecules) (43 – 45). Since the endothelium is one of the main constituents of the BBB, cilostazol may afford not only endothelial protection, but also BBB protection. These findings indicate that cilostazol may be a drug with the potential to reduce hemorrhagic complications via endothelial protection.

5. Concluding remarks

Anti-platelet therapies are widely used to decrease the risk of occlusive arterial events in patients with atherothrombotic risk, and meta-analyses have demonstrated the efficacy of antiplatelet therapies for secondary prevention following ischemic stroke. However, current antiplatelet therapies are accompanied by an increased hemorrhagic risk. Therefore, development of new antiplatelet agents that avoid hemorrhagic risk or derivation of combination therapies with endothelial protective agents will be expected in the future. Cilostazol may represent a promising candidate for pharmacological intervention in stroke based on its potential for endothelial protection.

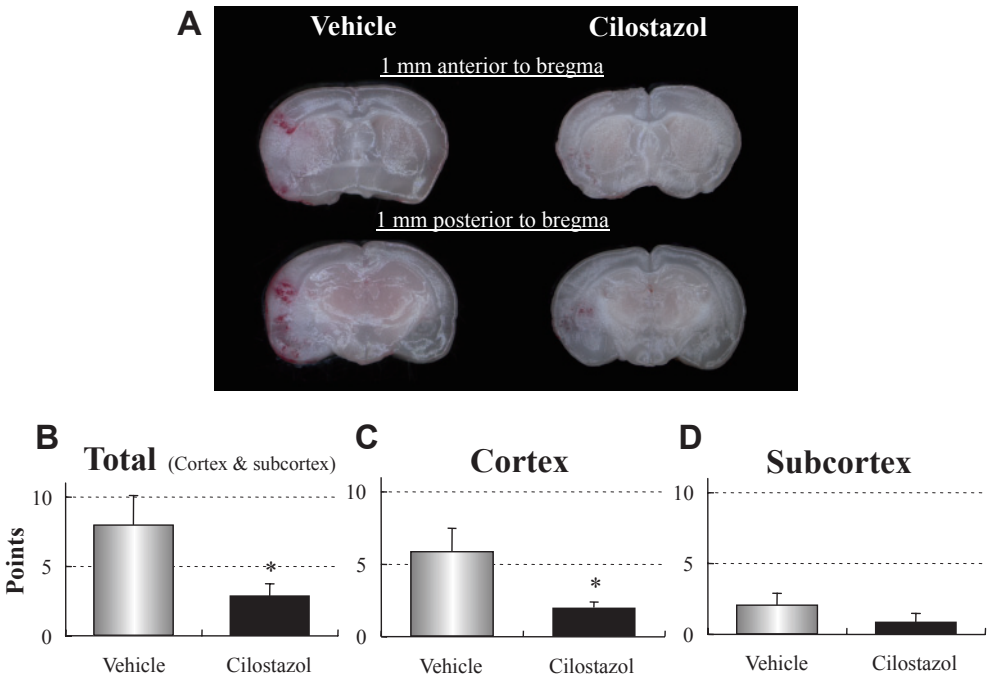

Fig. 2. Effect of cilostazol on hemorrhagic transformation at 22 h after a 2-h focal middle cerebral artery (MCA) occlusion in mice. A: coronal sections of brains from mice treated with vehicle (left) or cilostazol (right). Areas with staining (location ± 1 mm from the bregma) indicate hemorrhagic spots in the infarct area. Semi-quantitative analysis of hemorrhagic transformation by counting the number of hemorrhagic spots >500-μm diameter (one spot counting as one point). The average points in the total slice (B), cortex (C), and subcortex (D). *$P < 0.05$ vs. vehicle (Mann–Whitney U-test, n = 10). Data are expressed as the mean ± S.E.M. Modified from Neurosci Lett. (Ref. 41).

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