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Review

Classical and pleiotropic actions of dipyridamole: Not enough light to illuminate the dark tunnel?

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ABSTRACT

Dipyridamole is a platelet inhibitor indicated for the secondary prevention of transient ischemic attack. It inhibits the enzyme phosphodiesterase, elevates cAMP and cGMP levels and prevents platelet aggregation. Dipyridamole inhibits the cellular uptake of adenosine into red blood cells, platelets and endothelial cells that results in increased extracellular availability of adenosine, leading to modulation of cardiovascular function. The antiplatelet action of dipyridamole might offer therapeutic benefits in secondary stroke prevention in combination with aspirin. Inflammation and oxidative stress play an important role in atherosclerosis and thrombosis development, leading to stroke progression. Studies demonstrated anti-inflammatory, anti-oxidant and anti-proliferative actions of dipyridamole. These pleiotropic potentials of dipyridamole might contribute to improved therapeutic outcomes when used with aspirin in preventing secondary stroke. Dipyridamole was documented as a coronary vasodilator 5 decades ago. The therapeutic failure of dipyridamole as a coronary vasodilator is linked with induction of '*coronary steal*' phenomenon in which by dilating resistance vessels in non-ischemic zone, dipyridamole diverts the already reduced blood flow away from the area of ischemic myocardium. Dipyridamole at high-dose could cause a marked '*coronary steal*' effect. Dipyridamole, however, at low-dose could have a minimal hemodynamic effect. Low-dose dipyridamole treatment has a therapeutic potential in partially preventing diabetes mellitus-induced experimental vascular endothelial and renal abnormalities by enhancing endothelial nitric oxide signals and inducing renovascular reduction of oxidative stress. In spite of plenteous research on dipyridamole's use in clinics, its precise clinical application is still obscure. This review sheds lights on pleiotropic pharmacological actions and therapeutic potentials of dipyridamole.

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Introduction

Stroke is a leading cause of morbidity and mortality due to neurological disabilities in older individuals. Therapies that inhibit platelet activation are being employed to prevent recurrent stroke [1]. Dipyridamole was introduced in the early 1960s as a coronary vasodilator [2]. It inhibits platelet activation and reduces the thrombi formation. The antithrombotic property of dipyridamole makes a place for it to be used for secondary stroke prevention in combination with aspirin [2]. In addition to antithrombotic action, dipyridamole possesses beneficial actions in the vasculature that include direct and indirect effects on the endothelium such as inhibition of proliferation, anti-oxidant and anti-inflammatory actions [1]. Experimental evidence highlighted that dipyridamole could reverse the impairment of spatial working memory [2] whereas the protective effect of dipyridamole might have a link with its anti-inflammatory effect [2].

The use of dipyridamole is often limited for coronary artery disease because of the incidence of '*coronary steal*' phenomenon [3]. However, studies have shown that elevation of the extracellular adenosine levels induced by dipyridamole improves cardiac function in heart failure patients. Ikeda et al. [3] investigated whether the use of dipyridamole at the time of complete revascularization affects long-term mortality in patients with impaired left ventricular (LV) function. This study reported that the use of dipyridamole reduced both all-cause and cardiac mortality in patients with impaired LV function [3]. It has been evidenced that dipyridamole treatment reversed peripheral ischemia and induced angiogenesis in experimental diabetic condition by decreasing oxidative stress [4]. In addition, dipyridamole improved tissue nitric oxide (NO) bioavailability during experimental diabetic condition [4]. Likewise, dipyridamole augmented nitrite/NO production, leading to enhanced activity of arteriogenesis and blood perfusion in experimental ischemic limbs [5], suggesting that dipyridamole could augment ischemic vessel function and restore blood flow, which might be beneficial in peripheral artery disease [5]. A recent experimental study in rabbits suggested that dipyridamole treatment prior to stroke onset could significantly improve neurological outcome, cerebral hemodynamics and final infarct volume [6]. The pleiotropic anti-inflammatory and anti-oxidant actions of dipyridamole could contribute to some of its therapeutic benefits in improving vascular function and secondary stroke prevention. Moreover, studies also highlight the renoprotective potentials of dipyridamole [49,50]. This review will discuss the pleiotropic pharmacological actions and therapeutic potentials of dipyridamole.

Antiplatelet and vasodilatory actions of dipyridamole: mechanistic insights

Dipyridamole has diverse mechanism of action (Fig. 1). It principally inhibits the enzyme phosphodiesterase in platelets, and subsequently increases intraplatelet cAMP and cGMP levels, thereby inhibiting platelet aggregation and potentiating the platelet inhibitory actions of prostacyclin (PGI2) [7,8]. Dipyridamole inhibits cellular uptake and metabolism of adenosine, which also play a role in inhibiting platelet aggregation [8]. Dipyridamole-mediated increase in local concentration of adenosine might stimulate adenylyl cyclase in platelets, resulting in elevation of cAMP, which prevents platelet aggregation [7].

Upon increasing local adenosine level, dipyridamole can potentiate vasodilation. Dipyridamole enhances cGMP-dependent downstream vasodilatory effects in smooth muscle by inhibiting phosphodiesterase [7]. Dipyridamole-mediated increase in local concentration of adenosine could regulate vascular tone, inflammation and vasodilation [7]. The diverse mechanism of action of dipyridamole has been shown in Fig. 1.

Therapeutic implications of dipyridamole pertaining to its antiplatelet action: updates from recent clinical studies

The antiplatelet action of dipyridamole in combination with aspirin might offer therapeutic benefits in preventing secondary stroke and transient ischemic attack. Below we discussed and updated the relevant information with available clinical evidences.

Occlusive vascular events mainly include myocardial infarction, ischemic stroke and transient ischemic attack, occurring as a result of a reduced blood flow due to narrowness of artery, atherosclerosis and atherothrombosis. A meta-analysis by Verro et al. [9] systematically reviewed the randomized controlled trials comparing aspirin and dipyridamole combination with aspirin alone in patients with stroke and transient ischemic attack in order to determine their efficacy in preventing recurrent cerebral and systemic vascular events. This study revealed that the combination of aspirin and dipyridamole was more effective than aspirin alone in preventing stroke and other serious vascular events in patients with minor stroke and transient ischemic attack. The risk reduction was suggested to be greater and statistically significant for studies using primarily extended release dipyridamole, which was proposed to reflect a true pharmacological effect or lack of statistical power in studies using immediate release dipyridamole [9]. Another meta-analysis by Halkes et al. [10] from five clinical trials concluded that the combination of aspirin and dipyridamole was more effective than aspirin alone in patients with transient ischemic attack or ischemic stroke of presumed arterial origin in the secondary prevention of stroke and other vascular events [10]. A systematic review and economic analysis study assessed the clinical-effectiveness and cost-effectiveness of antiplatelets [11]. This study suggested that the most cost-effective treatment for patients with ischemic stroke/transient ischemic attack is clopidogrel, followed by modified-release dipyridamole and aspirin combination, followed by aspirin while patients with myocardial infarction is aspirin, followed by clopidogrel, and for patients with established peripheral arterial disease or multivascular disease is clopidogrel, followed by aspirin [11].

Dipyridamole alone might not be more efficacious than aspirin in patients who presented with arterial vascular disease [12]. Dipyridamole might however be effective in combination with other antiplatelet agents. The low-dose aspirin and dipyridamole combination was suggested to be more effective than aspirin alone in reducing the risk of recurrent stroke and other major cardiovascular events in patients with recent transient ischemic attack [13]. In the Second European Stroke Prevention Study (ESPS-2), addition of extended-release dipyridamole to low-dose aspirin, without significantly increasing the bleeding event, significantly reduced the risk of recurrent ischemic stroke [14]. Likewise, the European/Australasian Stroke Prevention in Reversible Ischemia Trial (ESPRIT) suggested that a combination of aspirin and extended-release dipyridamole was superior to aspirin alone in reducing the occurrence of primary combined end point of vascular death, nonfatal stroke, nonfatal myocardial infarction and major bleeding complications [14]. Importantly, aspirin plus extended-release dipyridamole and clopidogrel were suggested to be similarly effective for preventing recurrent stroke [15]. The safety of fixed-dose combination of aspirin and extended-release dipyridamole for stroke prevention in patients with ischemic heart disease was reviewed [16]. In this analysis, fixed-dose aspirin and extended-release dipyridamole were suggested not to be associated with an increased risk of cardiovascular events in patients with ischemic heart disease [16]. Moreover, extended-release dipyridamole was reported not to be associated with a higher number of cardiac events as compared to aspirin alone [16].

Pre-stroke treatment with a combination of low-dose aspirin and dipyridamole did not reduce the severity of acute stroke [17].