Review

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Aggrenox® (Extended-Release Dipyridamole and Low-Dose Aspirin in Combination): Protecting Platelets from Excessive Activation in Patients with Vascular Events

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Key Words
Aspirin · Dipyridamole · Aggrenox · Platelets · Activation

Abstract
Aspirin has become an established therapy in patients for preventing recurrent stroke and the incidence of acute coronary events. Aggrenox®, a novel combination of low-dose aspirin with dipyridamole, represents a safe and promising combination alternative for mild but sustained platelet inhibition and the reduction of occurrences of both arterial and venous thrombi. In a recent, large, well-controlled trial (European Stroke Prevention Study 2; ESPS-2) evaluating antiplatelet agents for stroke prevention, Aggrenox was twice as effective as either aspirin or dipyridamole. Results of experimental studies show that dipyridamole combined with aspirin at ratios of about 10:1 or higher effectively inhibit thrombus formation, whereas a ratio of 1:1 has little effect. Indeed, one of the reasons that the ESPS-2 trial appears so convincing was the fact that a high dose of extended-release dipyridamole was combined with low-dose aspirin at a dose ratio of 8:1. Combination therapy with Aggrenox inhibits platelet aggregation much more strongly than aspirin or dipyridamole alone, and it may gain an additional clinical benefit due to synergic targeting of leukocytes, through an increase in endothelial nitric oxide production. Based on in vitro data showing that platelet adhesivity and aggregation induced by adenosine diphosphate (ADP), adrenaline and collagen is diminished, as well as through measurements of malondialdehyde production (marker of free radical production), it is known that dipyridamole and aspirin indeed exhibit a potentiated synergism as platelet inhibitors. On the other hand, clopidogrel, a novel thienopyridine and a potent ADP receptor blocker, has also been proven to yield a clinical benefit in unstable angina patients and during coronary interventions. Considering recent trends to combine clopidogrel with aspirin, it remains to be seen which combination will better serve various clinical scenarios in the near future. Further well-designed and carefully conducted clinical trials should elucidate possible benefits of Aggrenox during coronary interventions, especially in conjunction with new and aggressive reperfusion techniques. The benefits of Aggrenox in an expanding array of clinical conditions, including ischemic stroke, may be directly related to platelet inhibition.

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Moreover, marginal clinical benefits and recently reported severe bleeding events in some patients after oral platelet glycoprotein IIb/IIIa therapy may advance Aggrenox as a safe and efficient alternative for patients with vascular disease. This review summarizes the latest and often confusing data on the effects of aspirin, dipyridamole and Aggrenox on platelets and attempts to relate these data to bleeding complications and clinical outcomes.

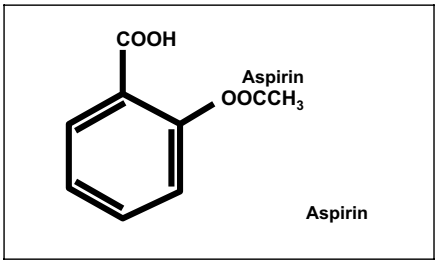

Fig. 1. Chemical structure of aspirin: acetylsalicylic acid (adapted from Devlin [117]).

Introduction

Coronary artery disease remains the leading cause of death and morbidity in the United States [1]. It afflicts 58 million Americans and it accounts for over 8 million hospital and emergency room visits and almost 1 million deaths annually [1, 2]. With advances in therapy, significant reductions in the morbidity and mortality associated with acute coronary syndromes have been achieved. Nevertheless, there is still significant room for improvement considering that the 30-day morbidity and mortality of acute coronary events continues to range from 7 to 20% [3–7].

Ischemic stroke is the third most common cause of death in the United States after heart disease and cancer [8]. Annually, there are over 500,000 victims of ischemic stroke, resulting in direct and indirect costs of over USD 50 billion [9].

Aspirin

Aspirin is one of the most commonly used drugs in the world. About 75,000 pounds of aspirin are consumed each day in the United States alone [10]. Aspirin is acetylsalicylic acid (fig. 1). Its antithrombotic effect is mediated through its acetylating and irreversible inhibition of cyclooxygenase (COX) (prostaglandin H synthesis), which is the initial enzyme in prostaglandin synthesis converting arachidonic acid to prostaglandin H_2 [11]. There are two known isozymes, COX-1 or prostaglandin H synthase-1 (PGHS-1) and COX-2 or PGHS-2. COX-1 is expressed in all cells throughout the body. It is responsible for the modulation of various physiological functions of prostaglandins such as controlling local tissue perfusion, hemostasis and protection of gastrointestinal tract mucosa. Conversely, COX-2 is induced only by certain stimuli (cytokines, growth factors, endotoxins) and serves to mediate defensive needs such as inflammation, immune reactions and mitogenesis [12]. Aspirin is a relatively selective inhibitor of COX-1, but does inhibit COX-2 at high concentrations as well [13, 14]. These basic findings have important clinical implications due to the differences in dosing when administering aspirin exclusively for its antiplatelet properties (low doses are sufficient) compared with its anti-inflammatory effects (high doses are required). Platelet synthesis of thromboxane A_2 (TXA2) and vascular endothelial cell synthesis of prostacyclin (PGI2) is impaired when COX-1 is inhibited and prostaglandin H_2 formation is blocked [15, 16]. Thus, aspirin is a unique agent with the potential to protect against both antithrombotic and thrombogenic events because TXA2 stimulates platelet aggregation and vasoconstriction, while PGI2 inhibits platelet aggregation and induces vasodilatation (fig. 2).

Other mechanisms have been postulated to explain the protective effects of aspirin against coronary and cerebrovascular disease. One such mechanism is the improvement of endothelial function. Thus, acetylcholine causes endothelium-dependent smooth muscle vasodilatation that is known to be mediated by the release of nitric oxide and endothelium-derived hyperpolarizing factor [17, 18]. This vasodilatory response to acetylcholine is blunted in patients with atherosclerosis or in those with atherosclerotic risk factors such as hypercholesterolemia, hypertension, diabetes and smoking [18–21]. This vascular defect has often been attributed to a depression of endothelium-derived relaxing factors. However, more recent studies of the acetylcholine response in patients with diabetes and congestive heart failure have implicated the role of a vasoconstricting factor that could be associated with COX activity [22, 23].

Measurements of the inhibition of platelet aggregation are used to quantify the effect of aspirin. The antiplatelet properties of aspirin are mediated by the inhibition of

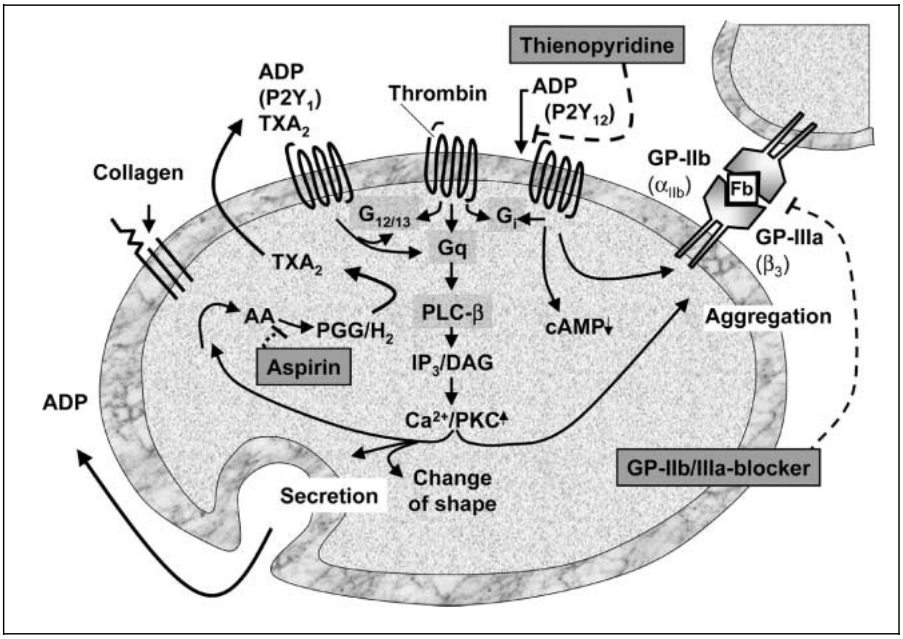

Fig. 2. Pathways and mechanisms of platelet inhibition (adapted from Devlin [117]). Platelet aggregation can be inhibited by GP IIb/IIIa antagonists, which prevent cross-linking via fibrinogen (Fb) to the GP IIb/IIIa complex on another platelet. Several platelet agonists such as ADP, thrombin, collagen and thromboxane may activate thrombocytes through specific receptor interactions, and the corresponding receptor antagonists act as platelet inhibitors. This is, for example, the case for thienopyridine compounds, which act on the ADP receptor. The antithrombotic effect of aspirin is mediated through its acetylating and irreversible inhibition of COX (prostaglandin H synthesis), which is the initial enzyme in prostaglandin synthesis converting arachidonic acid (AA) to prostaglandin H_2 (PGG/H_2). Intracellular pathways of activation are meditated through G proteins and phospholipase C (PLC), leading to the generation of inositol trisphosphate (IP_3) and diacylglycerol (DAG). Subsequently, protein kinase C (PKC) is activated, which together with elevated intracellular calcium levels triggers an altered shape of the thrombocyte as well as release of arachidonic acid. Arachidonic acid is oxygenated by COX (inhibited by aspirin) to PGG_2 and prostaglandin H_2, and finally altered to TXA2 through the enzyme thromboxane synthase. P2Y = Receptors which belong to the superfamily of G-protein coupled receptors with seven transmembrane domains.

COX resulting in decreased levels of PGI2 and TXA2 (fig. 2). Both are increased in the absence of aspirin, and elevated levels of TXA2 correlate with increased platelet aggregation. Urinary excretion of 6-keto-prostaglandin $F_{1\alpha}$ (a stable metabolite of PGI2) and thromboxane B_2 (TXB2; a metabolite of TXA2) were used to measure PGI2 and TXA2 formation. However, more recent studies have indicated that 11-dehydro-TXB2 (a metabolite of TXB2) [24–27] and 2,3-dinor-6-keto-prostaglandin $F_{1\alpha}$ (a metabolite of 6-keto-prostaglandin $F_{1\alpha}$) [28] are more stable and reliable indicators of platelet aggregation. Thus, numerous studies have measured the formation of these metabolites after administration of varying doses of aspirin to assess the efficacy of aspirin. However, speculations about the possibilities of assessing platelet function and eicosanoid synthesis on the basis of urinary excretion of prostanoids only are unconvincing. Thus, changes in urinary metabolites may be related to local renal secretion, increased metabolism and/or urinary excretion and do not necessarily reflect plasma concentration and synthesis.

Gastrointestinal side effects of aspirin are dose dependent and can be minimized with smaller doses and the usage of enteric-coated formulations. An increased incidence of abdominal pain, heartburn symptoms, nausea and occult gastrointestinal blood loss has been noted with aspirin at doses in excess of 900 mg/day [29]. Aspirin is rapidly absorbed in the stomach and upper intestine. Its half-life is only 15–20 min, plasma levels peak at approximately 30 min and meaningful platelet inhibition can be observed after 1 h. Because aspirin irreversibly inactivates COX, the duration of its platelet-inhibitory effect lasts for the life span of a platelet (approximately 10 days). Aspirin-mediated COX inhibition varies in platelets and vascular endothelial cells. COX synthesis is recovered in endothelial cells; thus, the duration of PGI2 inhibition by

aspirin and its thrombogenic potential is limited in time for endothelial cells [30, 31]. PGI2 production may also increase from once-daily dosing regimens of aspirin that allow recovery of COX-1 activity in vascular endothelial cells. It is established that the maximum efficacy of aspirin as an antithrombotic agent is at doses ranging from 160 to 320 mg/day [32]. However, the optimal aspirin dose is still under considerable debate. The center of this controversy relates to identifying a dosage of aspirin that inhibits TXA2 without blocking PGI2 synthesis. It has been demonstrated that the use of low-dose aspirin can inhibit both TXA2 and PGI2 production [33–35]. However, when very low doses of aspirin (30–75 mg/day) were studied, a selective inhibition of TXA2 without significant inhibition of PGI2 could be achieved [36–38].

The inability of aspirin monotherapy to protect from thrombotic vessel occlusion has been referred to as aspirin resistance or failure. It is not surprising considering the well-known fact that the antithrombotic effect of aspirin is mediated primarily through prostanoid blockade. In fact, there are several other potent inductors of platelet activation which exist independently from the prostaglandin pathway. These stimuli include adenosine diphosphate (ADP), thrombin, serotonin, platelet-activating factor and catecholamines. Interestingly, aspirin has been reported to exhibit antithrombotic effects independently from COX blockade, namely inhibition of platelet function [39–42] (fig. 2), enhancement of fibrinolysis [43, 44] and suppression of plasma coagulation [45–48]. Despite such a broad range of action, thrombosis still occurs in patients receiving antecedent aspirin therapy. COX-2 induction and activation of thromboxane-independent pathways of platelet aggregation are only two potential pharmacodynamic mechanisms. Indeed, over 90% inhibition of TXA2 formation is necessary for aspirin to produce an antithrombotic effect. Aspirin is capable of inhibiting COX-2, but not at usual clinical doses. In addition, aspirin-mediated COX-2 inhibition becomes blunted in individuals with atherosclerosis. An overall increase in TXA2 biosynthesis has been reported in patients with cardiovascular disease associated with endothelial dysfunction [49]. Importantly, the efficacy of aspirin is quite limited in the presence of shear stress, which is ultimately present in regions of compromised blood flow (i.e. acute occlusion or atherosclerosis). Shear stress-induced platelet activation is known to be independent of TXA2 formation [50, 51] and thus resistant to aspirin [52]. Other TXA2-independent stimulators of platelet activation, e.g. serotonin, thrombin, ADP and catecholamines [53], are unaffected by low and medium doses (60–500 mg daily) of aspirin [54]. Recently, aspirin-insensitive agonists of the platelet receptor, such as monocyte PGHS-2-derived TXA2 and F_2-isoprostane 8-epi-prostaglandin $F_{2\alpha}$ (a product of free radical-catalyzed peroxidation of arachidonic acid) have been described [55]. Unstable angina is associated with enhanced lipid peroxidation and reduced antioxidant defenses. The in vivo formation of F_2-isoprostane 8-iso-prostaglandin $F_{2\alpha}$, a bioactive product of arachidonic acid peroxidation, is enhanced in unstable angina and contributes to aspirin-insensitive thromboxane biosynthesis [56].

The pharmacokinetics of aspirin is suspected to vary between individuals, leading to an insufficient acetylation of COX in some patients. This has been demonstrated in clinical trials with low-dose aspirin [57, 58]. In fact, the antiplatelet effect of a fixed dose of aspirin is not constant over time in all individuals [59]. Possible pharmacodynamic explanations for insufficient antiplatelet effects of aspirin are the induction of (aspirin-resistant) COX-2 and a different sensitivity of hyperreactive platelets to aspirin, for example, subsequent to activation by thromboxane-independent pathways [48]. Some investigators have hypothesized that genetic polymorphism could result in differing gene expression of COX and thromboxane syntheses which could lead to aspirin resistance. Despite the 20% reduction in mortality at 5 weeks after treatment with 162.5 mg of aspirin per day after coadministration with streptokinase in patients with myocardial infarction [60] and nearly 50% reduction in death and myocardial infarction in patients with unstable angina [61–64], it is still a relatively weak inhibitor of platelet aggregation, and one that cannot fight the battle against acute ischemic coronary syndromes alone. Aspirin is an effective antithrombotic agent at doses between 75 mg and 1.2 g/day. It is also possible that 30 mg/day is effective. There is no evidence that low doses are either more or less effective than high doses when used over the long term, although doses less than 160 mg/day may not be effective acutely [65]. Aspirin therapy reduces stroke by 25% in most high-risk patients [32], but has no effect on those without clinically apparent vascular disease. A recent meta-analysis of 52,251 patients without any vascular disease enrolled in five clinical trials has shown that aspirin therapy was associated with a modest increase in the rate of stroke in three clinical trials, a decrease in one small trial and had no effect in the large clinical trials [66]. This contrasted with a highly significant reduction in myocardial infarction in these trials, with an overall rate of reduction of 26% [66]. Long-term use of aspirin therapy increased the incidence of hemorrhagic stroke both for those patients with and

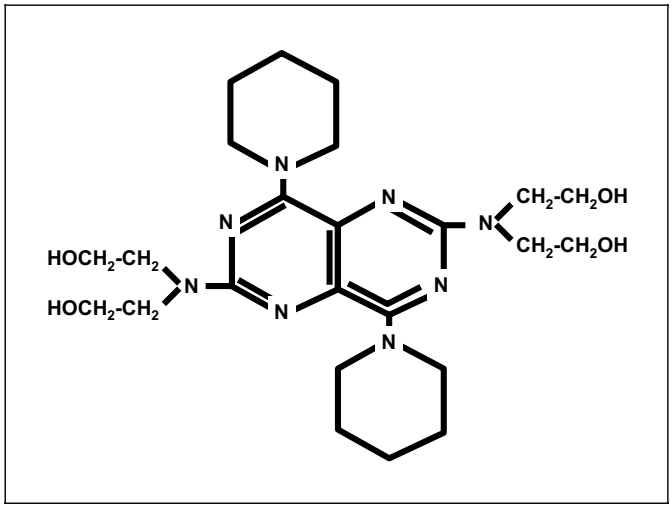

Fig. 3. Chemical structure of dipyridamole: 2,6-bis-(diethanolamino)-4,8-dipiperidino-pyrimido-(5,4-d) pyrimidine (adapted from Devlin [117]).

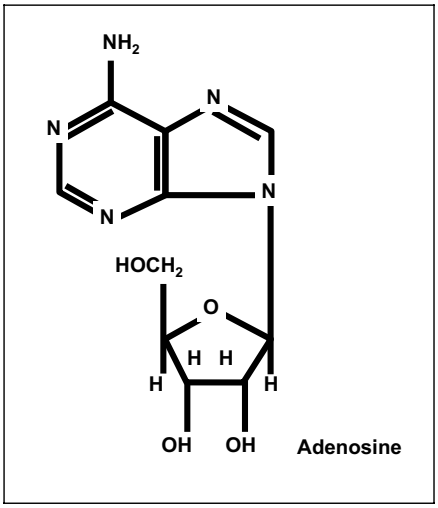

Fig. 4. Chemical structure of adenosine (adapted from Devlin [117]).

without manifest vascular disease. In one case-control study, aspirin at a dose of 1,225 mg/week or more was associated with a 3-fold increased rate of intracranial hemorrhage, while no increase was observed with lower doses [67].

Dipyridamole

Dipyridamole is an antiplatelet agent chemically described as 2,6-bis-(diethanolamino)-4,8-dipiperidino-pyrimido-(5,4-d) pyrimidine (fig. 3). At therapeutic concentrations (0.5–1.9 μg/ml), dipyridamole inhibits the uptake of adenosine (fig. 4) into platelets, endothelial cells and erythrocytes in vitro and in vivo in a dose-dependent manner. Such inhibition results in an increase in adenosine, which targets platelet A_2 receptors (fig. 5). As a result, stimulating platelet adenylate cyclase activity leads to increased platelet cyclic-3′,5′-adenosine monophosphate (cAMP) levels. Via this mechanism, platelet aggregation is inhibited in response to various stimuli such as platelet activating factor (PAF), collagen and ADP (fig. 2). Dipyridamole inhibits phosphodiesterase (PDE) in various tissues. At the therapeutic level, dipyridamole inhibits cyclic-3′,5′-guanosine monophosphate (cGMP)-PDE, thereby augmenting the increase in cGMP produced by endothelium-derived relaxing factor (now identified as nitric oxide) [68, 69].

Dipyridamole also stimulates tissue adenosine levels. Elevated intramyocardial concentrations of adenosine induced by dipyridamole lead to epicardial coronary artery dilatation [70]. Coronary vasodilatation with high-dose intravenous dipyridamole is associated with significant relative redistribution of blood flow to collateral-dependent myocardium in patients with severe heart disease [71]. Indeed, excessive vasodilatation can lead to a worsening of ischemia. These findings resulted in the use of dipyridamole for pharmacological stress testing. The usual dose of a 'provocation' with dipyridamole is very high (0.56 or 0.82 mg/kg over 4 min), and it seems understandable that cardiologists avoid or at least are reluctant to use dipyridamole for the treatment of coronary artery disease.

However, convincing evidence linking adenosine to angiogenesis raises the possibility of a therapeutically relevant anti-ischemic effect of the drug [72]. Adenosine (fig. 4), released in increased amounts by hypoxic tissues, is thought to be an angiogenic factor that links altered cellular metabolism caused by oxygen deprivation to compensatory angiogenesis. Adenosine interacts with 4 subtypes of G protein-coupled receptors, termed A_1, A_{2A}, A_{2B} and A_3 (fig. 5). Thus, the A_{2B} adenosine receptor subtype appears to mediate the actions of adenosine to increase growth factor production, cAMP content and cell proliferation. Adenosine activates the A_{2B} adenosine receptor in vascular endothelial cells, leading to neovascularization

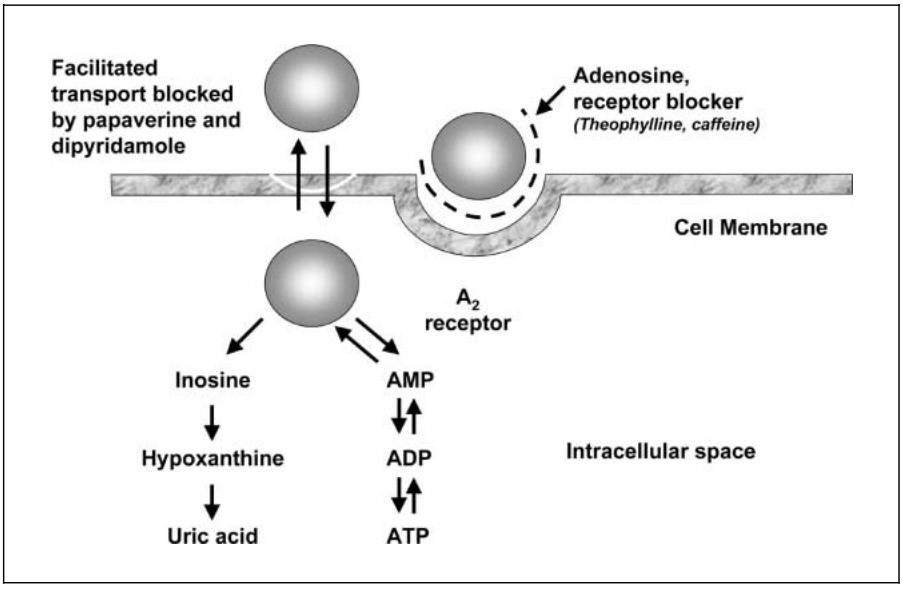

Fig. 5. Mechanisms of action of adenosine (adapted from Devlin [117]). Adenosine, a naturally occurring purine, is produced in small amounts as part of normal cellular metabolism by dephosphorylation of adenosine monophosphate (AMP) and intracellular degradation of S-adenosyl-homocysteine. Adenosine is released from the cell upon formation. Extracellular adenosine accumulates and binds to cell surface A_1 and A_2 purine receptors, where it is thought to induce vasodilation. Vasodilation is related to the inhibition of the slow inward calcium current, thus reducing calcium uptake, and activation of adenylate cyclase by A_2 receptors in smooth muscle cells. Adenosine may also lessen vascular tone by modulating sympathetic neurotransmission. Methylxanthines such as caffeine and theophylline are competitive antagonists of adenosine, competing for A_2 cell surface receptor sites. As such, adenosine vasoactivity is reduced in the presence of these substances. Dipyridamole blocks the facilitated adenosine transport into the cell.

by a mechanism involving increased angiogenic growth factor expression [73]. The available data support the 'adenosine collateral hypothesis' (i.e. a beneficial, angiogenesis-promoting effect of chronic endogenous adenosine accumulation). Dipyridamole, a potent inhibitor of nucleoside transport into cells, has recently been reported to stimulate the proliferation of capillary endothelial cells in the heart and skeletal muscle of rats following long-term treatment [74, 75]. Morphologic data indicate that chronic, intermittent dipyridamole administration increases endomyocardial capillary length density by 33% in hypertensive and 11% in normotensive rabbits [76]. Experimental data suggest that chronic treatment with dipyridamole increases collateral flow and decreases exercise-induced left ventricular dysfunction in the territory dependent upon a critical coronary stenosis. Meta-analyses of clinical data from all published double-blind, placebo-controlled, randomized trials assessing the effect of dipyridamole as an antianginal agent showed a highly significant drug benefit [77–79]. Intriguingly, treatment duration correlated significantly with the observed benefit, supporting the concept of a structural change in the collateral coronary circulation requiring time to emerge. In one trial, repeated intravenous administration of adenosine and heparin could mimic physiologic angiogenesis and reduce the amount of exercise-induced myocardial ischemia in patients with coronary artery disease [80]. There was indeed a 9% reduction in the extent (60.6 ± 4.0 vs. 54.9 ± 4.1 [arbitrary perfusion defect units], $p = 0.03$) and a 14% improvement in the severity (41.5 ± 3.2 vs. 35.7 ± 2.9 [arbitrary color intensity change units], $p = 0.01$) of the myocardial perfusion abnormalities on the perfusion scans seen in patients who received adenosine and heparin compared with a placebo. Thus, in this pilot study, repeated administration of adenosine and heparin reduced the amount of exercise-induced ischemia in patients with chronic stable angina that remained refractory to conventional treatment [80].

Moreover, there is angiographically supported evidence that intravenous dipyridamole not only affects the coronary circulation, but also results in a significant reduction of the incidence of abrupt vessel closure following coronary interventions [81]. This significant reduction was observed in patients presenting with stable angi-

na as well as in those who underwent angioplasty for acute coronary syndromes. Regarding secondary clinical end points, intracoronary administration of dipyridamole did not affect the need for bypass grafting or the incidence of death following angioplasty. Intracoronary application of dipyridamole was also associated with a reduction in myocardial infarction following intervention [81]. In another study, it was shown that patients tolerated significantly longer durations of balloon inflation with intracoronary administration of dipyridamole than did patients in the control group [82]. The severity of chest pain and extent of electrocardiographic signs of ischemia were significantly lower after intracoronary administration of dipyridamole as well. The reductions in chest pain and ST segment shift caused by intracoronary administration of dipyridamole during the first balloon inflation were even more pronounced than the protection that was afforded by the third balloon inflation for patients in the control group [82]. Another elegant study showed that intracoronary dipyridamole reduces the incidence of adverse cardiovascular events in the first 48 h after balloon angioplasty of small coronary arteries [83].

Dipyridamole clearly enhances the dilatation caused by exogenous nitric oxide from four different sources, including endothelial cells [84], and reduces the threshold for platelet suppression by nitric oxide via inhibition of cGMP-PDE [85]. Clinical benefits with dipyridamole may be attributed not only to platelet inhibition, but also to some aspects of leukocyte activity. Dipyridamole effectively inhibits superoxide anion generation by neutrophils and mononuclear leukocytes through an increase in extracellular adenosine that in turn inhibits both superoxide anion generation by leukocytes and the expression of procoagulant activity by mononuclear leukocytes [86]. Unfortunately, the data on how dipyridamole affects adhesion molecules are very limited [87]. One animal study has shown that dipyridamole remarkably prevents endothelial P-selectin expression in the vascular beds [88]. Another report suggests that after dipyridamole administration in stress testing, the level of soluble adhesion molecules (vascular cell adhesion molecule-1, E-selectin and L-selectin) could be elevated [89].

Aggrenox

Aggrenox® is a combination antiplatelet agent intended for oral administration. Each hard gelatin capsule contains 200 mg of dipyridamole (fig. 3) in an extended-release form and 25 mg of aspirin (fig. 1) as an immediate-release sugar-coated formulation. The nature of the effectiveness of such a combination is not fully understood. However, there are some reasonable explanations for this phenomenon. Earlier studies using high-dose aspirin in combination with dipyridamole found no additional benefit yielded when compared with monotherapy [90–92]. Strong evidence from preclinical studies suggests that a high dose of aspirin may directly interfere with the action of dipyridamole. Results of experimental studies show that dipyridamole combined with aspirin at ratios of about 10:1 is much more effective in inhibiting thrombus formation, whereas a ratio of 1:1 has little or no effect [87, 93]. The first European Stroke Prevention Study (ESPS-1) compared the outcomes of 2,500 patients who suffered from previous cerebrovascular disorders treated with acetylsalicylic acid plus dipyridamole or matched placebo and followed them up for 2 years. Treatment was associated with a 33.5% reduction in the incidence of all end points (death from all causes or strokes) by an intention-to-treat analysis and a 36.5% reduction by explanatory analysis [94]. The end point reduction appeared to be similar in men and women. The effect of treatment was similar regardless of the patients' age, the nature of the qualifying cerebrovascular event, the site of the responsible lesion and diastolic blood pressure. However, the efficacy of aspirin or dipyridamole alone and the most effective acetylsalicylic acid dosage still remained unknown after ESPS-1. Therefore, a second trial (ESPS-2) was conducted that included treatment arms of aspirin alone, dipyridamole alone, combination therapy and placebo [95]. The combination of aspirin 25 mg plus extended-release dipyridamole 200 mg twice daily was shown in the ESPS-2 to be significantly better than either agent given individually in preventing stroke and transient ischemic attacks. A low-dose aspirin (50 mg/day) regimen produced a significant risk reduction of 18% for stroke and 13% for stroke and/or death in pairwise comparisons, but no reduction in all-cause mortality. The sustained-release dipyridamole produced a significant risk reduction of 16% for stroke and 15% for stroke and/or death. In combination, aspirin and dipyridamole produced a risk reduction of 37% for stroke and 24% for stroke and/or death [96]. Importantly, ESPS-2 evaluated a high dose of extended-release dipyridamole combined with low-dose aspirin at a dose ratio of 8:1. This specific dosing combination produced an added inhibitory effect on platelet activation compared with placebo or either drug alone [97], supporting the clinical outcome data. Aspirin and dipyridamole significantly increase antiplatelet properties via an increase in nitric oxide production [98]; these results provide further evi-

dence of the therapeutic benefits of the combination approach. In addition, inhibition of platelet adhesion and aggregation and reduction of malondialdehyde production (marker of free radical production) are the biochemical events in which dipyridamole and aspirin show potentiation [99].

Risk of Bleeding

The initial studies of intravenous glycoprotein (GP) IIb/IIIa inhibitors in acute coronary syndromes showed that adverse clinical events and subsequent morbidity can indeed be reduced with these agents. The major limitation to the expansion of this class of agents is a need to maintain a delicate balance between the reduction of ischemia and the high incidence of life-threatening bleeding complications including hemorrhagic stroke. Recent disasters with numerous oral GP IIb/IIIa blockers raised caution in clinicians even further. Agents other than direct IIb/IIIa inhibitors can specifically inhibit platelet activity, but to a lesser degree. The effect of combinations or compounds such as Aggrenox, novel thienopyridines and recently discovered selective serotonin reuptake inhibitors [100] as potent and safe adjuncts may have particular benefits, and these may directly threaten the survival of oral GP IIb/IIIa blockers. Besides bleeding, there are some other major concerns that remain unresolved with the use of chronic GP IIb/IIIa inhibitors. Issues have been raised regarding the consistency of platelet inhibition (high peaks and low troughs), which could affect the occurrence of thrombotic events. Although the mean level of platelet inhibition looks appealing, individual data reveal marked variability in the levels of inhibition produced by these agents [101]. These findings may explain periods of inadequate protection and enhanced bleeding risks over the course of therapy in a single patient. The other important issue is that inhibition of GP IIb/IIIa is not an exclusive property of the agents specifically targeting this platelet receptor. Clopidogrel [102] and aspirin [103] mildly inhibit GP IIb/IIIa as well, which challenges the unique nature of GP IIb/IIIa blockers. Still, the biggest problem with modern antiplatelet strategies is the incidence of major bleeding. For instance, among patients randomized to placebo or eptifibatide and enrolled in the Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy (PURSUIT) trial in the United States, discontinuation of the study drug infusion occurred more frequently in the eptifibatide treatment group because of bleeding complications, which occurred almost nine times more often in the eptifibatide group (17.5% of patients) as compared with the patients receiving placebo (2%) [104]. Combined therapy of abciximab and thrombolysis has also been shown to increase the risk of hemorrhages [105, 106] by a factor of at least 3.

Abciximab, but not eptifibatide or tirofiban, increases the incidence of thrombocytopenia [107] and pseudothrombocytopenia [108] compared with placebo in patients also treated with heparin. Not surprisingly, patients with thrombocytopenia had significantly higher rates of major bleeding, profound decreases in hemoglobin and increased transfusion requirements of both blood and platelets compared with those without thrombocytopenia [109].

Currently, clopidogrel is becoming one of the most widely used medications for the prevention of acute vascular events. When clopidogrel (75 mg) was compared with aspirin (325 mg) in the Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events (CAPRIE) study, bleeding was uncommon, and the frequency of any bleeding event was similar for aspirin and clopidogrel (9.27 vs. 9.28%) [110]. There was a trend towards a lower incidence of intracranial hemorrhage in the clopidogrel group (0.31%) compared with the aspirin group (0.42%). Any reported gastrointestinal hemorrhage was significantly less frequent with clopidogrel (1.99%) than with high-dose aspirin (2.66%) [111]. Nevertheless, the major adverse effect of the drug, observed in the recent Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial, was still bleeding. Major bleeding episodes increased by 33%, from 2.7% in the aspirin-only group to 3.6% in the clopidogrel and aspirin group [112].

In pooled data received from five randomized trials (with 52,251 participants randomized to aspirin doses ranging from 75 to 650 mg/day), the risk of intracranial hemorrhage was increased by the regular use of aspirin (relative risk = 1.35; $p = 0.03$), similarly for both primary and secondary prevention [113, 114]. The combination of dipyridamole and aspirin prevented 2.82 strokes at the expense of an excess risk of 0.61 fatal or severe bleeds per 100 treatment-years, while aspirin prevented 1–2 vascular events per 100 treatment-years with an excess risk of fatal and severe bleeds of 0.4–0.6 per 100 treatment-years [66]. Hypothetically, the combination of dipyridamole and aspirin could represent an ideal medication that moderately suppresses expression of GP IIb/IIIa but does not profoundly block other receptors and proteins, thus diminishing the risk of bleeding complications [115].

Conclusion: In Search of the 'Ideal' Antiplatelet Agent

Blood platelets play a major role in normal hemostasis and in the development of occlusive thrombotic disorders. Acquired platelet dysfunction affects both short- and long-term outcome in patients with vascular events. Therefore, inhibiting platelet function is an important therapeutic goal. The role of antiplatelet therapy in the acute treatment and prevention of acute coronary events is huge. Aspirin is effective in the acute treatment and secondary prevention of acute coronary syndromes. However, it is still a relatively weak inhibitor of platelet aggregation and one that cannot fight the battle against acute ischemic coronary syndromes alone. The constant attempts to find an ideal agent to prevent platelet activation in the clinical setting surrounding acute vascular events has become of critical importance over the last 2 decades. At the same time, the combination of aspirin and dipyridamole seems very promising, particularly after the results of ESPS-2. Moreover, marginal clinical benefits and recently reported severe bleeding events in some patients after oral platelet GP IIb/IIIa therapy [116] may advance Aggrenox as a safe alternative and efficient moderate adjunct for the treatment and prevention of vascular events. Since dipyridamole plus aspirin reduces the risk of stroke by 23% over aspirin alone, one should further explore such a promising combination in patients with coronary artery disease. Hence further well-designed and carefully conducted clinical trials should elucidate the potential benefits of Aggrenox in multiple thrombotic conditions, including myocardial infarction, stroke and unstable angina.

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