Antiplatelet Therapy in Acute Cerebral Ischemia

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Background—Improved recognition of stroke signs and symptoms has paralleled the development of pharmacological strategies that may be examined to reduce stroke mortality and morbidity. Presently, tissue plasminogen activator is the only therapy that significantly improves outcome in acute stroke, with no agent demonstrating a significant reduction in mortality.

Summary of Review—Antiplatelet agents are a heterogenous class of drugs that have been successfully used for more than 2 decades in secondary stroke prevention. These agents include aspirin, with or without dipyridamole, and more recently, the adenosine antagonists ticlopidine and clopidogrel. However, studies of the use of antiplatelet agents within 48 hours of the ictus have examined only aspirin. Only 1 study, the Multicentre Acute Stroke Trial–Italy (MAST-I), entered patients within 6 hours of the ictus. These data suggest that an improvement in mortality may be related to the speed of administration. No significant adverse events were noted with early antiplatelet monotherapy. However, MAST-I did note a significant increase in early mortality in patients receiving aspirin plus streptokinase, a finding not adequately explained by an increase in the intracranial hemorrhage rate.

Conclusions—The use of antiplatelet therapy in acute stroke, clinical or experimental, has only recently received attention. It is likely that the use of antiplatelet agents for acute stroke therapy will be less restrictive than that currently seen for thrombolytics. Future studies should include an examination of those agents that have previously demonstrated efficacy in secondary stroke prevention, most notably, aspirin. The recognition that all platelet stimuli share a final common pathway that is dependent on the surface glycoprotein IIb/IIIa (fibrinogen) receptor has resulted in the development of various agents which block this receptor and are currently the focus for clinical trials. The role of nitric oxide in stroke therapy will depend on minimizing the hypotensive side effects of this agent. Stroke models are needed to provide preliminary data on the efficacy of antiplatelet therapy, especially as relates to the interaction of antiplatelet agents with thrombolytics. (Stroke. 1999;30:887-893.)

Key Words: antiplatelet therapy ■ aspirin ■ cerebral infarction ■ stroke, acute

Pharmacological strategies to reverse or minimize acute ischemic brain injury include “antiplatelet” agents, anticoagulants, and thrombolytics. Historically, antiplatelet therapy is the most recently utilized.1-4 Despite the overwhelming success of this therapy for the treatment of acute myocardial ischemia over the last decade,5,6 antiplatelet therapy for acute stroke has received little attention until very recently. The general reluctance to use any therapeutic strategy for the treatment of acute cerebral ischemia likely reflects the long-standing nihilism, which argued that the therapeutic window of time for stroke was too narrow to realistically expect that any intervention could improve the natural history of the disease. This philosophy surfaced in the early 1960s, when attempts to treat stroke with thrombolytics and anticoagulants resulted in an increased mortality rate.3 At that time, there was both a very limited understanding of the pathophysiology of stroke and an absence of animal stroke models to study the effects of various therapies for the treatment of acute cerebral ischemia. Since these early stroke trials, 3 major advances have allowed the nihilism surrounding stroke therapy in the 1960s to be replaced by the cautious optimism of the 1990s.

The first of these advances was an improved understanding of the pathophysiology of stroke. In the early 1980s, the window of time for neuronal salvage following the initiation of acute cerebral ischemia was established for a nonhuman primate model.3 In this study, the concept of intensity-duration of cerebral ischemia was established. That is, the greater the intensity of the ischemic event, the less time is necessary to demonstrate the same degree of permanent injury. In retrospect, the previous clinical treatment of stroke had used time frames as late as 24 to 48 hours, whereas these more current concepts suggested a maximal time frame for treatment in the range of 6 hours. The second advance was the successful use of antiplatelet agents and thrombolytics in acute myocardial infarction (MI).5,6 Despite the early failures of thrombolytics in the

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treatment of acute stroke, the mortality in acute MI was significantly reduced through the use of acute thrombolytic therapy as well as by aspirin monotherapy. Moreover, the combination of the 2 therapies was additively beneficial. Finally, the third major advance was the development of animal stroke models, which greatly assisted in defining acute stroke mechanisms and therapeutic strategies. These animal models also proved useful in refining the therapeutic window of time as well as the overall duration of treatment.

The importance of antiplatelet agents for both the prevention and treatment of ischemic disease was a concept that developed as the consequence of a trial of research breakthroughs in the 1960s: (1) recognition of the contribution of platelets to both cardiac and carotid disease, and (2) development of reproducible assays to quantify platelet activation, and (3) demonstration that “anti-inflammatory” agents inhibit platelet aggregation. The mechanism by which aspirin inhibited platelet aggregation awaited further clarification in the mid 1970s with the dual discoveries that (1) platelets, thrombocytes, produce a very potent lipid, an arachidonic acid (AA) metabolite possessing an oxane ring, that results in aggregation and vasoconstriction: thromboxane (TX) and (2) aspirin irreversibly acetylates the cyclooxygenase enzyme responsible for the metabolism of AA to TX and other prostaglandins.

It has been nearly 25 years since aspirin therapy was first demonstrated to be clinically efficacious for secondary stroke prevention. Although it is now well established that antiplatelet monotherapy using either aspirin or adenosine receptor antagonists such as ticlopidine is clearly efficacious in reducing neurological sequelae/recurrent events following a TIA or stroke, the examination of antiplatelet agents as monotherapy for the treatment of acute cerebrovascular ischemia has received little attention either clinically or experimentally.

In contrast to the clinical treatment of strokes (acute and subacute), which has focused primarily on aspirin therapy, antiplatelet therapies for animal models of acute cerebrovascular ischemia have generally focused on either (1) very specific alterations of the AA cascade, attempting to either increase levels of the vasodilator/platelet inhibitor prostacyclin (PGI2) or reducing the level/activity of the vasoconstrictor/platelet proaggregant thromboxane A2 (TXA2) or (2) serotonin (5-HT3) receptor antagonism. These therapies have produced variable results. It is also of interest that several studies employing the prophylactic use of aspirin for stroke prevention in “low-risk” patients have reported either no benefit or an increase in stroke incidence. These studies correlate well with earlier clinical observations that aspirin possesses antifibrinolytic and/or thrombotenic effect(s).

Antiplatelet therapy has also been recently combined with thrombolytics for the treatment of acute cerebrovascular ischemia. These studies are a logical extension of the therapeutic strategies first examined for the treatment of acute MI nearly a decade earlier. The use of an adjuvant therapy to thrombolytics appeared to be both necessary (optimal reperfusion with thrombolytic agents occurs in less than 50% of treated patients, and the urgency associated with the brief 3-hour window of time for the clinical treatment of acute stroke) and, based on the additive benefit seen with these 2 agents in acute MI, very promising, even though the efficacy of aspirin in acute MI may actually relate to the prevention of vessel reocclusion rather than an improvement in the coronary artery patency rate.

Experimental studies combining thrombolytic therapy with antiplatelet agents are extremely limited and have not demonstrated a consistent effect on brain injury (infarct size or hemorrhage), although 1 study noted an increased rate of intracranial hemorrhage with high-dose aspirin therapy in rabbits. Mechanisms to explain the findings in this latter study were not examined, although the dose of tPA used (10 mg/kg) may have been supramaximal.

Specific examination of the effect of antiplatelet therapy on the rate of reperfusion with thrombolytics has been examined by the coadministration of a TX receptor antagonist and a tPA congener in a middle cerebral artery model of photodynamic (nonembolic) injury. Dual therapy improved both the patency rate and reduced infarct size when compared with thrombolytic therapy alone; however, the anatomic and pathologic findings following photo-illumination injury are difficult to relate to the clinical state of thromboembolic stroke. Conversely, recent studies in our laboratory have demonstrated that aspirin, but not ticlopidine, antagonizes tPA-mediated clot lysis in a dose-related manner in a rabbit model of thromboembolic stroke, a finding which was reversed by nitric oxide (NO) donors, the prostacyclin mimetic iloprost, and both the β-1 antagonist atenolol and hydralazine.

The specific mechanism by which aspirin may antagonize clot lysis is unclear. However, the common denominator in these studies is the ability of each of these agents to improve regional cerebral blood flow (rCBF) by approximately 20%, whereas the administration of aspirin (20 mg/kg) resulted in an acute reduction in rCBF of approximately 20%. Of great interest, the Multicentre Acute Stroke Trial-Italy (MAST-I), a clinical trial of streptokinase with or without concomitant aspirin therapy, concluded that the group receiving streptokinase plus aspirin had a marked increase in the 10 day fatality rate that could not be adequately explained by an increase in intracranial hemorrhages.

Thus, the benefit, if any, of antiplatelet therapy for the treatment of acute cerebrovascular ischemia, either clinically or experimentally remains unclear, although it does appear that aspirin monotherapy may result in a modest clinical improvement. Overall, this limited data suggests both (1) an incomplete understanding of and (2) diverse and/or multiple mechanisms of action for “antiplatelet” agents. For example, the 5-HT3 receptor subtype is found not only on platelets where it is responsible for aggregation, but also in vascular smooth muscle and in cerebral cortex where its actions include vasoconstriction and neuronal excitation, respectively. Thus, any examination of antiplatelet drugs in acute stroke must recognize the hetero-
Arachidonic Acid Cascade
Although aspirin is thought to have multiple mechanisms of action,\textsuperscript{44–47} it has been generally accepted that its effectiveness in ischemic states relates to a directed imbalance of the AA cascade.\textsuperscript{19} That is, at low doses (1 mg/kg), aspirin may differentially inhibit the production of the potent vasoconstrictor and platelet activator TXA\textsubscript{2} relative to prostacyclin, a vasodilator and platelet inhibitor.\textsuperscript{48} However, it is of interest that clinical trials examining prostacyclin infusions within 24 hours of the ictus did not improve neurological outcome versus placebo.\textsuperscript{49} The MAST-I study is the only randomized clinical study to date that administered an antiplatelet agent (aspirin) within 6 hours of the ictus. At both 10 days and at 6 months, a trend toward a reduction in mortality was seen with aspirin therapy. Two large-scale, randomized, prospective clinical trials, the International Stroke Trial (IST)\textsuperscript{2} and the Chinese Acute Stroke Trial (CAST),\textsuperscript{3} have recently been completed in which aspirin (300 and 160 mg daily, respectively) was administered within 48 hours of the ischemic event. These 2 studies reported slight reductions in either recurrent ischemic events or in mortality. Although the benefit seen with aspirin was very modest, its ease of administration, wide availability, and low cost argue for its use in the setting of patients who are not candidates for thrombolytic therapy or of clinical trials examining other antiplatelet agents.

Although aspirin therapy has been conclusively shown to reduce both the incidence of and mortality from MI irrespective of the dose administered,\textsuperscript{50} there is considerable controversy surrounding the optimal dose of aspirin for stroke prevention following TIA.\textsuperscript{51–54} Indeed, it has been suggested in some, but not all, clinical studies that high-dose (15 to 20 mg/kg) aspirin therapy may be more effective than low-dose aspirin in preventing stroke after TIA, although this finding is counterintuitive to the known effects of aspirin on the AA cascade, since the production of both TXA\textsubscript{2} and prostacyclin is completely inhibited at these higher doses.

Adenosine Receptor Antagonists
The P2 purinoceptor is activated physiologically by adenosine diphosphate, which may be released from red blood cells and the endothelium as well as from the platelet-dense granules (the latter important for amplification of the platelet aggregation process). The development of adenosine receptor antagonists such as ticlopidine and clopidogrel has allowed for a new mechanistic strategy for ischemic disease states.

Ticlopidine and, more recently, clopidogrel have received considerable attention for secondary stroke prevention, demonstrating a trend toward greater efficacy for stroke prophylaxis than aspirin,\textsuperscript{51,54} although the differences in outcome for aspirin therapy versus ticlopidine or clopidogrel are slight. This may also relate to the effects of ticlopidine on the AA cascade, as it may reduce levels of TXA\textsubscript{2} while actually increasing those of prostacyclin.\textsuperscript{55} To date, neither ticlopidine nor clopidogrel has been examined in an acute time frame (<6 hours) in acute ischemic stroke.

Serotonin (5-HT\textsubscript{2}) Receptor Antagonists
Serotonin activates platelets via the 5-HT\textsubscript{2} receptor located on the cell surface, contributing to the genesis of arterial thrombi.\textsuperscript{56} Although serotonin is suggested to be a weak agonist in isolation, an amplification process in concert with other agonists has been described, such that inhibition of both the 5-HT\textsubscript{2} and TXA\textsubscript{2} receptors results in an additive benefit in models of coronary thrombolysis. In experimental models of acute cerebral ischemia, 5-HT\textsubscript{2} receptor antagonists have produced variable results.\textsuperscript{25,26} Although not yet examined acutely in clinical stroke, the delayed clinical use of 5-HT\textsubscript{2} receptor antagonists after stroke has resulted in improved functional status.\textsuperscript{57} Despite the success of combined thrombolytic therapy with 5-HT\textsubscript{2} receptor antagonists in both coronary\textsuperscript{63} and peripheral thrombosis,\textsuperscript{58} this strategy has not yet been examined after stroke.

Phosphodiesterase Inhibition
Adenosine 3',5'-cyclic monophosphate (cAMP) is an important modulator of platelet function. A reduction in cAMP may result in platelet aggregation. A variety of mediators, including prostacyclin and phosphodiesterase inhibitors such as dipyridamole, may function to inhibit platelet aggregation by increasing cAMP. A number of clinical trials have examined dipyridamole in secondary stroke prevention,\textsuperscript{59,60} with the recent European Stroke Prevention Study 2 (ESPS-2) demonstrating improved outcome/event reduction with dipyridamole (400 mg daily) or aspirin (30 mg daily) monotherapy, with the combination of aspirin plus dipyridamole affording additive benefit.

GP IIb/IIIa Receptor Antagonists
Platelet activation and aggregation can occur by pathways independent of the AA cascade, as demonstrated with low-dose thrombin and with platelet activating factor.\textsuperscript{61} All of these mechanisms share a final common pathway dependent on the surface glycoprotein IIb/IIIa complex (GP IIb/IIIa). Fibrinogen is the ligand for the GP IIb/IIIa receptor and is responsible for amplification of the aggregation response.\textsuperscript{62} The GP IIb/IIIa receptor may be blocked by either peptides exhibiting the amino acid binding sequence RGDF (arginine-glycine-aspartic acid-phenylalanine\textsuperscript{63}; eg, integrilin, tirofiban, lamifiban) or monoclonal antibodies (eg, ReoPro [abciximab]). GP IIb/IIIa receptor interference has demonstrated greater potency than aspirin in preventing thrombosis and rethrombosis in animal models of coronary\textsuperscript{64,65} and carotid\textsuperscript{66} artery stenosis. Recent clinical studies examining integrilin in acute MI have also demonstrated improved reperfusion.\textsuperscript{67}
Nitric Oxide

NO, a short-lived and reactive chemical intermediate, is receiving considerable attention for its contribution to the cerebrovascular circulation during both physiological and pathological states. Although NO is not specifically an antithrombotic agent, it does possess antithrombotic and vasodilator properties similar to those of prostacyclin. Both the substrate for NO (L-arginine) and NO donors (3-morpholinosydnonimine [SIN-1], sodium nitroprusside, nitroglycerine) have reduced ischemic and ischemia-reperfusion injury in a variety of organ systems. Moreover, NO inhibits thrombotic events and interacts synergistically with thrombolytics to improve outcome during experimental cardiac and peripheral ischemia. Indeed, the discovery of NO has begun to provide a more mechanistic explanation for the benefit of nitrates and possibly other agents in acute myocardial ischemia, as NO exerts negative inotropic/chronotropic actions and reduces blood pressure. Beta-receptor antagonists have been demonstrated to facilitate NO release, possibly contributing to their benefit in acute MI. Although the efficacy of beta-receptor blockade in acute MI is thought to be afforded through a reduction in the cardiac workload, beta-blockade has been demonstrated to synergize with the thrombolytics, presumably through their ability to improve collateral flow.

The role of NO in acute stroke has relied almost exclusively on rat models of permanent focal ischemia. For acute cerebral ischemia there is a general consensus that endothelial NO is beneficial. Early administration of a NO source within the vascular compartment reduces brain injury, while nonspecific NO synthase (NOS) inhibitors in acute ischemia exacerbate brain injury, perhaps by reducing rCBF. Conversely, the delayed administration of NO has generally resulted in an increase in ischemic brain injury.

Neuronal NO may be deleterious in models of cerebral ischemia, possibly by participating in glutamate-mediated neurotoxicity. Of interest, NO sensors have demonstrated increased levels of intracerebral NO in acute stroke, particularly during the ischemic episode, with smaller elevations noted during reperfusion. Moreover, inhibitors directed at either neuronal NOS (7-nitroindazole) or inducible NOS (iNOS; aminoguanidine) reduce brain injury in models of permanent focal cerebral ischemia. Supporting the concept that eNOS and nNOS may serve as a contrast for reducing and exacerbating ischemic tissue injury, respectively, is the recent development of “knock-out” mice. In each circumstance, the deletion of the enzyme results in the predicted outcome: greater ischemic injury in mice devoid of eNOS and less-than-anticipated injury in mice without nNOS.

The production of NO and the cyclooxygenase products of the AA cascade, prostaglandins (particularly prostacyclin), appear to be closely linked in many biological systems. That is, in many but not all experimental models, the upregulation/stimulation of NO will result in an increase in eicosanoid production, such as prostacyclin. Conversely, changes in prostacyclin levels result in similar effects on NO production or activity. Of great interest, aspirin and, to some extent, other cyclooxygenase inhibitors, have demonstrated inhibition of inducible NOS activity. Thus, previous studies focusing on either NO or the AA cascade in isolation may need to reexamine these findings in order to gain a more comprehensive understanding of the mechanism of action. Specifically, aspirin inhibition of both NO and prostacyclin could result in adverse effects on thrombolysis, such as the antagonism of clot lysis recently demonstrated in a rabbit model of thromboembolic stroke. It was hypothesized that the antagonism of clot lysis seen in this model may be abrogated by the concomitant administration of agents that either stimulate or provide a source of NO. These studies demonstrated that addition of NO donors to aspirin therapy reversed the antagonism of tPA-mediated clot lysis seen with aspirin administration. This finding may help to explain the disparate results obtained among the various ischemic models and clinical scenarios that have included aspirin, particularly cardiac versus cerebral ischemia.

Future Directions

Recognizing that the timing of therapy will impact efficacy, future studies should emphasize treatment initiated within 6 hours of the ictus. To date, MAST-I is the only prospective, randomized clinical study to examine an antithrombotic agent, aspirin, within this time frame. Although the results demonstrate a promising and persistent trend in reducing mortality, larger studies are needed to confirm these findings. Based on the success of ESPS-2 in secondary stroke prevention, a logical extension of these studies includes the combination of aspirin plus dipyridamole. Alternatively, MAST-I emphasizes that combining therapeutic strategies such as aspirin and streptokinase may adversely affect outcome and should first be carefully studied in appropriate animal models.

The development of GP IIb/IIIa antagonists and inhibitors has demonstrated efficacy in myocardial ischemia without the side effect of significant bleeding. Future directions in acute stroke management should include an examination of this promising antithrombotic therapy. There is also much interest in understanding the role of NO in acute stroke therapy. Similar to prostacyclin, NO may reduce ischemic injury through suppression of platelet and/or neutrophil activation. The vasodilator and hypotensive effects of prostacyclin likely contributed to its lack of efficacy in earlier stroke trials and raise appropriate concerns about the role of NO in this setting. However, the ability to deliver NO by inhalation may abrogate its hemodynamic side effects and allow further examination of this novel therapy in acute stroke.

In summary, antithrombotic drugs represent a diverse group of agents that share the ability to reduce platelet activity through a variety of mechanisms. Their biological activities go well beyond the platelet and include effects both locally on other blood elements and within the vessel wall as well as more remote effects on other cell types throughout the body. It is recognized that the intact endothelium
produces a variety of substances, including NO, tPA and prostacyclin, that are physiologically important to the local blood flow, as well as ensuring both the maintenance of a nonthrombogenic surface and facilitating local clot lysis. As noted, “antiplatelet” agents such as aspirin may affect both NO and prostacyclin levels, with resultant adverse effects on exogenous tPA therapy. It is also recognized that the clinical use of tPA as a monotherapy for acute stroke will remain limited. However, it is also clear from the cardiac literature that adjutant therapy, particularly antiplatelet agents, can enhance the efficacy of thrombolysis and improve outcome. The future use of antiplatelet therapy for the treatment of acute cerebral ischemia is dependent on a greater understanding of the activity of these agents not only on platelet function but also on the cerebrovasculature and within the brain parenchyma, especially as they relate to cerebral blood flow, the blood-brain barrier, and neuronal function. These examinations will assist in determining the most beneficial pharmacological regimen that will minimize brain injury in acute stroke.

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