Antiplatelet agents, carotid endarterectomy, and perioperative complications

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Neurosurgeons are frequently involved in choosing an antiplatelet therapy for their patients in the perioperative period. New data obtained from the Aspirin and Carotid Endarterectomy (ACE) Trial suggest that low-dose aspirin is superior to high-dose aspirin therapy in reducing rates of perioperative stroke and death. The ACE-related data are reviewed, and the authors provide an update on current Food and Drug Administration–approved antiplatelet therapies for secondary stroke prevention, as well as a summary of antiplatelet therapies being developed.

KEY WORDS • antiplatelet agent • carotid endarterectomy • perioperative complication

Neurosurgeons frequently play a key role in the choice of stroke-prevention therapy. Their role is paramount in patients undergoing evaluation for CEA. Antiplatelet therapy is the mainstay in the prevention of secondary stroke in most patients in whom a cardioembolic source is not found. Therefore, in addition to selecting appropriate candidates to undergo CEA, neurosurgeons may need to choose medical therapy that reduces the risks of perioperative stroke and death. Two recent developments in the treatment of cerebrovascular disease may directly affect such choices. First, new prospective, randomized data on aspirin dosing obtained in a CEA populations are now available. Second, physicians now have more choices for the use of antiplatelet therapy in the prevention of stroke that include several different mechanisms of action.

ANTIPLATELET THERAPIES

Platelet adhesion is thought to play an integral role in the development of symptomatic cerebrovascular disease.²⁸ Figure 1 provides an illustration of the sites of action for commonly used antiplatelet agents. The mechanism of aspirin's antiplatelet activity has been well characterized and is thought to work predominantly through its inhibition of cyclooxygenase. Exposure of collagen during CEA has been suggested as a strong stimulus to platelet aggregation.²⁴ This has led to an interest in examining the use of aspirin in the perioperative period.

Abbreviations used in this paper: CEA = carotid endarterectomy; FDA = Food and Drug Administration; MI = myocardial infarction.

Aspirin Therapy

Aspirin is the only antiplatelet drug to be well studied in populations of patients undergoing CEA. Based on a subgroup analysis of the North American Symptomatic Carotid Endarterectomy Trial studies,^{2,30} a differential effect of high- compared with low-dose aspirin on perioperative stroke and death was suggested. This was in part supported by earlier positive studies in which patients received high-dose aspirin (> 1g) post-CEA^{6,26} and one negative study in which very low-dose aspirin (50 mg) was used.⁸ Analysis of other data has indicated that low-dose aspirin (75 mg) was effective in preventing recurrent stroke after CEA.²¹

The Aspirin and Carotid Endarterectomy (ACE) Trial³⁰ was a prospective, randomized double-blinded, controlled trial of low-dose (81-mg or 325-mg) and high-dose (650-mg or 1300-mg) aspirin therapy in patients undergoing CEA. This international study enrolled 828 patients scheduled for CEA with both symptomatic (46%) and asymptomatic (54%) carotid artery stenosis that was greater than or equal to 60%. All participating surgeons reported 30-day stroke and death rates of up to 6%. Patients were randomized to one of four dosage groups approximately 2 days prior to surgery. The patients were followed for 3 months postoperatively, and a combined outcome of stroke, MI, and death was compared between the lower-dosage tiers (81 mg or 325 mg) and the higher-dosage tiers (650 mg or 1300 mg) in a prespecified primary analysis. Baseline characteristics including type of surgeon and technique used were similar among the four groups. In the lower-dosage group lower postoperative

Granule release is influenced by the intracellular concentrations of cyclic adenosine (cAMP) and cyclic guanine monophosphate (cGMP). Agonists, particularly collagen and thrombin may have direct effects on granule release, and both thromboxane A2 and intracellular Ca²⁺ concentration can have direct effects on IIb/IIIa receptor exposure promoting aggregation. A: The site of aspirin's blockade of cyclooxygenase. B: The sites of action of the thienopyridines (ticlopidine and clopidogrel). C: The site of action of dipyridamole by increasing intracellular cyclic nucleotides. D: The receptor that is blocked by IIb/IIIa antagonists.

In a recent study in patients undergoing CEA the authors did not find perioperative aspirin use to be an independent risk factor for postoperative hematoma formation.²⁷ However, with only 29 cases of postoperative

Ticlopidine and clopidogrel are FDA-approved agents used in the prevention of secondary stroke. These chemically related compounds are both thienopyridines and inhibit platelet aggregation by similar mechanisms.

Antiplatelet agents

Ticlopidine^{15,17} has been shown to be superior to aspirin in reducing recurrent stroke, but its clinical use has been limited because of its safety profile. Recently, an additional concern about potentially fatal thrombotic thrombocytopenic purpura has been identified.^{3,5,10} Early recognition and treatment with plasmapheresis has been shown to improve survival.⁵ Although the exact risk is unknown, an estimate based on available data is one per 2000 cases treated.³¹ The risks of this and other ticlopidine use-related complications need to be weighed against potential benefits.

Clopidogrel has been shown to reduce MI, stroke, and vascular disease-related death in patients who have suffered recent stroke, recent MI, or in whom there is established peripheral arterial disease.⁹ Since the drug received FDA approval, the manufacturer estimates that 1.5 million people have been exposed to clopidogrel (D. Kargman and C. Sekaran, Sanofi-Synthelabo Inc., personal communication). Continued postmarketing surveillance for adverse events including blood dyscrasia is ongoing.

The recent FDA approval of combination extended-release dipyridamole and very low-dose aspirin has added a fourth agent to our antiplatelet armamentarium.¹³ In a very large clinical trial, this combination therapy was shown to have a statistically significant effect on reducing the risk of recurrent stroke, but it did not affect the rate of MI or death.¹¹ There is some conflicting data on the use of regular dipyridamole in patients undergoing CEA.^{12,16} No additional studies of this combination or the newer extended-release formulation in CEA patients were found in our search of the literature.

Other antiplatelet agents such as IIb/IIIa antagonist therapy can be potentially used for the prevention of stroke in both those who have already suffered stroke and those undergoing CEA. However, to date, no published studies conducted in humans were found to support the use of these in either of the aforementioned populations. Concerns over severe thrombocytopenia²² and marked increased bleeding risk⁷ have been raised regarding this class of agents and may limit their use in a CEA population. Clinical trials in which investigators are examining the safety and efficacy of oral IIb/IIIa antagonists in stroke patients are ongoing.

Combination therapies also hold promise as potentially superior aggregation blockades that may lead to our improved ability to prevent stroke. The thienopyridines have been studied in conjunction with aspirin in other vessel-related procedures such as placement of coronary stents^{19,23} and have been widely used in these populations because of the proven²⁰ or perceived²⁹ superior antiaggregant effects of combination therapy over aspirin alone. No combination therapies other than dipyridamole and aspirin have been reported in patients undergoing CEA.

CONCLUSIONS

The recently published ACE data suggest that in patients undergoing CEA, reduced perioperative stroke and death rates occur when receiving low-dose aspirin (< 325 mg) as compared with high-dose aspirin treatment (> 650 mg). Although these remain the only randomized, blinded, controlled data obtained in the perioperative period in

patients undergoing antiplatelet therapy in CEA patients, there are now several other FDA approved antiplatelet agents. Surgeons need to be aware of the potential risks and benefits of each of the antiplatelet agents as they relate to CEA and secondary stroke prevention. Additional research is needed to identify the optimum secondary stroke prevention therapy in the perioperative period and beyond.

ADDENDUM

Since this work was submitted, two recent articles have been published that provide additional information on antiplatelet therapy. A randomized, double-blind, placebo-controlled dose-escalation study of abciximab, a IIb/IIIa antagonist, in 74 ischemic stroke patients has been recently published.¹ The patients were treated with placebo or one of four doses of abciximab. It was suggested that the 0.25-mg/kg bolus and 12-hour infusion regimen be submitted for further safety and efficacy evaluation.

An early release of an article by Bennett, et al.,⁴ has been made available on the New England Journal of Medicine Web page (<http://www.nejm.org/content/bennett/1.asp>). The authors describe 11 cases of thrombotic thrombocytopenic purpura in patients who were receiving or had recently received clopidogrel, out of an estimated three million individuals exposed to it. They recommended that physicians be aware of the possibility of thrombotic thrombocytopenic purpura among patients receiving clopidogrel.

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