Antiplatelet Medications in the Secondary Prevention of Ischemic Stroke

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Current Neurology and Neuroscience Reports 2005, **5:**1–3
Current Science Inc. ISSN 1528-4042

Introduction

Given its potentially disabling nature and burdensome numbers, ischemic stroke (IS) has long been a target for improved therapy. We have learned much regarding risk factors for IS and their potential treatments in the past few decades. However, I would like to direct my comments to the current status of medical therapy for the secondary prevention of IS. What prompted my choice of topics? The recent publication of new clinical trials made my decision. In discussing these trials with medical students and residents in the context of patient care, I began to wonder if we really have made that much progress in our options for medical therapy. Certainly, this commentary is not a comprehensive review of all medications used in the secondary prevention of all types of IS. These overview comments are directed to the care of patients with IS who have no definite indication for warfarin anticoagulation or revascularization procedures such as carotid endarterectomy or angioplasty/stenting.

A Brief History of Medications in the Secondary Prevention of Ischemic Stroke

We have known the benefit of aspirin, a cyclooxygenase inhibitor, in the secondary prevention of IS since the 1970s [1,2]. In the 1980s, ticlopidine was introduced as a novel antiplatelet agent that blocked the adenosine diphosphate pathway of platelet aggregation. Ticlopidine (500 mg/d) was found to be more effective than aspirin (1300 mg/d) at preventing strokes in patients with recent transient ischemic attacks (TIA) or IS [3], although this effectiveness does not seem to apply to black patients [4]. Unfortunately, ticlopidine's side effects, including neutropenia and thrombotic thrombocytopenic purpura, made it difficult to use.

In the 1990s, clopidogrel was introduced. It was chemically related to ticlopidine and inhibited platelet aggregation in the same way but with less risk of severe hematologic side effects. The Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) study [5] showed that patients with atherosclerotic vascular disease manifest by IS, myocardial infarction, or symptomatic peripheral vascular disease had a lower annual risk of IS, myocardial infarction, or vascular death if they took 75 mg/d of clopidogrel (5.32%) versus 325 mg/d of aspirin (5.83%). The absolute risk reduction was small (0.51%) but was statistically significant given the large number of patients enrolled, which was approximately 20,000. For patients who entered the study with strokes, the average event rate favored clopidogrel but was not statistically significant (7.15% vs 7.71%).

In 1996, the results of the European Stroke Prevention Study 2 (ESPS2) [6] were published. In this study, which randomized patients with a history of TIA or stroke, the combination of low-dose aspirin (50 mg/d) and modified-release dipyridamole (400 mg/d) was found to be more effective than aspirin alone in preventing recurrent stroke. Not all studies have shown a proven benefit of the combination of aspirin and dipyridamole over aspirin alone, but these had fewer patients than ESPS2 and used different doses of these medications [7,8].

Warfarin was also compared with aspirin in the prevention of recurrent ischemic stroke in the Warfarin Aspirin Recurrent Stroke Study (WARSS) [9] published in 2001. No difference between aspirin (325 mg/d) and warfarin (International Normalized Ratio of 1.4 to 2.8) was found in the prevention of recurrent IS or death or in the rate of major hemorrhage [9].

New Clinical Trials

Based on this information, the three major medications used in the secondary prevention of IS are aspirin, clopidogrel, and aspirin/dipyridamole. Perhaps it would make sense to combine aspirin and clopidogrel. Their mechanism of antiplatelet activity is different and perhaps the combination would be more effective than either alone. After all, the combination of aspirin and clopidogrel seemed to be effective in preventing vascular events in patients with acute coronary syndromes and following percutaneous coronary interventions [10,11]. Why shouldn't it work well at preventing recurrent IS?

The Management of Atherothrombosis with Clopidogrel in High-risk patients (MATCH) study [12] was recently published. This randomized, double-blind trial compared aspirin (75 mg/d) plus clopidogrel (75 mg/d) with clopidogrel in 7566 high-risk patients with IS or TIA and at least one additional vascular risk factor. A nonsignificant 1% absolute risk reduction (15.7% vs 16.7%) in favor of the combination therapy was noted for the composite endpoint of IS, myocardial infarction, vascular death, or rehospitalization for acute ischemia (*eg*, TIA, angina pectoris, or worsening peripheral arterial disease). Unfortunately, life-threatening bleeding occurred twice as often in the combination-therapy arm (2.6% vs 1.3%). Major bleeding episodes were also increased in the combination-therapy arm. No overall difference in mortality was noted. Based on these data, it appears that adding aspirin to clopidogrel is not beneficial and may increase bleeding complications in patients with IS or TIA and vascular disease.

Other ongoing clinical trials are also evaluating the usefulness of the combination of aspirin and clopidogrel. The Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management and Avoidance (CHARISMA) trial [13] is one of them. This industry-sponsored trial plans to enroll over 15,000 patients worldwide. Patients may be enrolled if they have a combination of vascular risk factors or documented cerebrovascular disease, coronary artery disease, or symptomatic peripheral arterial disease. They will be randomized to receive aspirin (75 to 162 mg/d) plus clopidogrel (75 mg/d) or placebo. The primary outcome is a combined endpoint of cardiovascular mortality, stroke, or acute myocardial infarction.

It would be most interesting to see data from trials directly comparing the efficacy and safety of the combination of aspirin and clopidogrel versus the combination of aspirin and dipyridamole. The Prevention Regimen For Effectively avoiding Second Strokes (PRoFESS) trial [14] was originally planned to do just this. This industry-sponsored trial was planning to randomize over 15,000 patients with ischemic stroke into one of two groups: aspirin and dipyridamole or aspirin and clopidogrel. Half of the patients in each group were also going to receive telmisartan, an angiotensin receptor blocker. However, when the results of the MATCH study were released, the Steering Committee decided to discontinue the aspirin component of the clopidogrel plus aspirin–treatment arm. This was recommended by the Data Safety Monitoring Board because of the increased risk of life-threatening and major bleeding noted in the MATCH trial. On the other hand, not all ongoing trials using the combination of aspirin and clopidogrel have chosen to amend their protocol. The Secondary Prevention of Small Subcortical Strokes (SPS3) trial [15] is designed to determine if the combination of aspirin (325 mg/d) plus clopidogrel (75 mg/d) is more effective than aspirin alone at preventing recurrent stroke in patients with a lacunar or small subcortical stroke. In addition to differing antiplatelet regimens, participants will also be randomized into two different levels of blood pressure control to see if this influences recurrent stroke rate. Although clearly a more restricted patient population, the information gathered by this study will be helpful in evaluating the combination of aspirin and clopidogrel.

Cost

The cost of medications does play a potential role in decisions regarding medical therapy. This may be especially true in the population at highest stroke risk, namely the elderly. I decided to call three different drug stores (representing three large nationwide chains) in the Indianapolis, IN area to find out the cost of 1 month's supply for a person with only Medicare coverage paying out-of-pocket for medications. The cost of 30 tablets of clopidogrel (75 mg) ranged from $105 to $151. The cost of 60 tablets of aspirin (25 mg) and dipyridamole (200 mg) ranged from $118 to $141. The cost of 30 tablets of aspirin (325 mg) was approximately $0.25 and the cost of 30 tablets of enteric-coated aspirin (325 mg) was approximately $1.00 to $1.50.

Conclusions

It is difficult to make general statements regarding choices in the medical management of patients with IS given its multiple mechanisms and individual patient variations. It is exceedingly important to manage all vascular risk factors in each patient, especially hypertension. Managing risk factors is as important as, or perhaps more important than, deciding on a prevention medication. Based on the previous discussion, I present my recommendations for antiplatelet secondary prevention of noncardioembolic IS.

1. Aspirin, typically 325 mg/d, remains my first choice for those taking no antiplatelets at the time of their stroke. It is effective, relatively safe, and inexpensive. It has also been proven effective in other forms of vascular disease, especially coronary artery disease.
2. For those patients allergic to aspirin, 75 mg/d of clopidogrel is a reasonable alternative.
3. For those patients already taking aspirin at the time of their IS, either 75 mg of clopidogrel or 25 mg of aspirin and 200 mg of dipyridamole twice daily are reasonable choices. The results of the PRoFESS trial may prove that one of these is a better choice.
4. The combination of aspirin and clopidogrel for the secondary prevention of stroke seems risky based on the results of the MATCH trial. However, further data from ongoing clinical trials may alter the perceived risk/benefit ratio of this combination.

5. Ongoing clinical trials will further refine the indications for various antiplatelet medications in specific subtypes of ischemic stroke.

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