Prophylactic Neuroprotection for Cerebral Ischemia

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Background Treatments for acute ischemic stroke have evolved as knowledge about the pathophysiology of ischemic brain injury has advanced. Treatment strategies under development are aimed at offering neuroprotection acutely after focal cerebral ischemic injury, but delayed initiation of therapy may reduce efficacy. Pretreatment before ischemia begins could offer distinct advantages in patient groups at high risk for ischemic stroke.

Summary of Review If a neuroprotective drug were available orally, safe, and relatively inexpensive, it could be considered for prophylactic use in high-risk populations. Prophylactic neuroprotection would include (1) short-term neuroprotection before and after high-stroke risk procedures, (2) long-term neuroprotection for primary and secondary intervention in populations at high risk for stroke, and (3) concomitant neuroprotection with agents that have multiple treatment effects. Patients undergoing procedures such as cardiac surgery, endarterectomy, or endovascular therapy, which have a risk of cerebral ischemic events during a defined period, might be considered for short-term, periprocedure prophylactic neuroprotection. Several populations at high long-term risk for initial ischemic stroke have been identified and include those with combinations of vascular risk factors, transient ischemic attacks, atrial fibrillation, and asymptomatic carotid stenosis. Such people, as well as those at risk for stroke recurrence after minor strokes, are readily identifiable and perhaps appropriate for long-term prophylactic neuroprotection. Patients with hypertension and cerebrovascular atherosclerosis have a high stroke risk, and therapies directed at these underlying disorders are available that also have concomitant neuroprotective effects. An ideal drug for trials in these patient groups has not yet been developed, and establishing its efficacy may prove to be an arduous and lengthy task.

Conclusions The possibility of ameliorating the consequences of an acute ischemic stroke by pretreating high-risk patients with appropriate neuroprotective agents needs to be explored. Several types of high-risk population for prophylactic neuroprotection can be envisioned and then studied in clinical trials. (Stroke. 1994;25:1075-1080.)

Key Words • cerebral ischemia, focal • neuroprotection • risk factors

A major aim set by Public Health Services in the United States and United Kingdom is to reduce the mortality from stroke.1 Accomplishing these aims will require the development of effective treatments for stroke and focused primary and secondary prevention. A growing area of research involves the use of drugs to protect the brain from ischemia by limiting cell injury and death, thereby reducing morbidity and mortality from stroke. We have assembled our concepts of prophylactic, pharmacologic neuroprotection against the background of the following definitions. (1) Focal (including multifocal) brain ischemia is brain ischemia resulting from occlusion by a local process (eg, thrombosis or dissection) in a cerebral or intracranial artery supplying the brain or from emboli entering the arterial circulation of the brain from the heart, proximal aorta, or cervical arteries. (2) Neuroprotection means enhancing the tolerance of the cell bodies and processes of brain neurons and glia to ischemia and ultimately promoting functional recovery. (3) By pharmacologic means we mean the use of drugs that have a protective effect by direct action on the described cells and their processes. That pharmacologic neuroprotection is possible in the absence of complete restoration of normal blood flow is a belief implicitly based on the assumption that the organism has endogenous protective and reparative mechanisms such as collateral circulation or new synapse formation, beneficial effects of which can be enhanced by early exogenous interference with the ischemic cascade.

Neuroprotection from cerebral ischemic injury is likely to be accomplished most effectively if pretreatment with a safe and effective drug is feasible. The concept of prophylactic neuroprotection is derived from observations that, with many drugs, pretreatment in animal stroke models yields better outcomes than post-onset treatment and the suggestion from clinical trials that very early treatment after stroke may be necessary. For most patients with acute ischemic stroke, pretreatment is unrealistic because a large group of people would have to take medication for an extended period of time to afford an opportunity for prophylaxis in a select few. The risk-benefit ratio under such conditions is likely to be narrow at best. However, some subgroups of patients are at substantial risk for ischemic stroke during either a brief or extended period, and it is for these subgroups that prophylactic neuroprotection might offer an attractive treatment approach.

Pharmacologic Approaches to Prophylactic Neuroprotection

Prophylactic pharmacologic neuroprotection assumes that safe, efficacious, orally available, and relatively...
inexpensive drugs will be developed. Designing effective neuroprotective agents for focal ischemic injury is dependent on a detailed comprehension of the pathophysiological events that mediate the process. Large strides toward this goal occurred during the past decade. One important potential approach to acute stroke treatment, reperfusion therapy, is not tenable as a method for prophylaxis and protection, although when considered most broadly, prophylactic antithrombotic therapy with anticoagulants or platelet antiaggregants might be seen as contributing to reperfusion by reducing initial thrombus formation. Neuroprotective therapies are directed at the biochemical and metabolic, cellular consequences of focal ischemic injury. A variety of these ischemic cellular derangements have been elucidated and others await discovery. The neuroprotective therapies currently most widely evaluated are those related to antagonism of voltage- and receptor-mediated calcium channels and antioxidant therapies directed at inhibiting the consequences of oxygen free radical–mediated cellular injury. Additional strategies for neuroprotection from ischemic injury that have been less extensively evaluated include presynaptic modulation of excitatory amino acid release, sodium channel antagonists, adenosine enhancers, calcain inhibitors, polyepptide growth factors, and interruption of mediators of programmed cell death. In vitro and in vivo animal data document the cytoprotective effects of these approaches. Interestingly, for many voltage- and receptor-mediated calcium channel antagonists, treatment initiated shortly before the ischemic insult appears to afford better protection than treatment after ischemia. Such observations discourage the idea that prophylactic neuroprotection might have value. However, pretreatment for extended periods before stroke onset has not been performed with most purported neuroprotectants in animal stroke models. Once neuroprotective effects with an agent are documented with acute intervention, short- or long-term prophylactic therapy can be assessed in animals to model human trials. Such an approach would provide information about toxicity, dosing, and effectiveness to help guide human trial organization.

Nimodipine, a member of the dihydropyridine class of voltage-sensitive calcium channel antagonists, was evaluated in several large clinical trials of acute ischemic stroke. Although the overall results were negative, a meta-analysis suggested that early treatment, within 12 hours of stroke onset, might be effective. Combined with animal data showing greater effectiveness of nimodipine when given before ischemia begins, these observations suggest that nimodipine or a related calcium antagonist might be a candidate for prophylactic neuroprotection in an appropriate patient group. Additionally, many voltage-sensitive channel antagonists have antihypertensive and antiatherogenic effects, as demonstrated in animal atherosclerosis models and preliminary human trials. Thus, an appropriate voltage-sensitive calcium channel antagonist might prevent atherosclerotic plaque progression and protect the brain from ischemic injury.

Competitive and noncompetitive antagonists of the N-methyl-D-aspartate (NMDA)–mediated calcium channel have shown promise for reducing ischemic lesion size in animal stroke models, and several of these agents are now in clinical trial. Dextromethorphan and memantine are presently available noncompetitive NMDA antagonists that can be given orally and have a tolerable side-effect profile. Felbamate, a new anticonvulsant, is a glycine site antagonist with neuroprotective qualities. The long-term safety of felbamate appears to be acceptable, and the beneficial effects are obtained at well-tolerated doses. Therefore, these drugs along with other NMDA antagonists might be appropriate candidates for prophylactic neuroprotection. Other glutamate-mediated channels, such as the a-amino-3-hydroxy-5-methyl-4-isoxazole (AMPA) channel, metabotropic channel, and kainate channel, may also be appropriate targets for prophylactic antagonists. Concerns about the long-term administration of NMDA and other glutamate-mediated channel antagonists need to be considered. Many of these agents have toxic side effects involving the cardiovascular system, memory, and psychotomimetic effects. Neuropathologic changes have been seen, although vacuolization observed with dizocilpine may be transient. These side effects will have to be monitored if the drug is advanced to preliminary human trials before an NMDA antagonist can be considered for a prophylactic neuroprotection trial. Inherent difficulties with long-term use of NMDA antagonists may arise because inhibiting these or other glutamate-responsive channels may impede normal brain function such as synaptic transmission, learning, and plasticity.

The 21-aminosteroids are potent antioxidants with proven effects to reduce ischemic lesion size in animal models without glucocorticoid or mineralocorticoid side effects. Tirilazad, a 21-aminosteroid, is currently in clinical trial. Although tirilazad can only be given intravenously, other potent antioxidants are being developed that can be orally administered. Antioxidants may also impede atherogenesis, as suggested in animal studies, perhaps in relation to interfering with low-density lipoprotein cholesterol oxidation, an apparently important step in plaque development. Thus, antioxidants may offer another mechanism of dual benefit, ie, reducing stroke risk and neuroprotection. As previously mentioned, several additional neuroprotective approaches are at earlier stages of development, and it is possible that additional potential drugs for prophylactic neuroprotection will emerge from this group.

**Candidates for Prophylactic Neuroprotection**

With the availability of potentially effective and safe neuroprotective agents, populations that might benefit must be identified and then studied in appropriate clinical trials. Three major categories can be anticipated. First, the short-term neuroprotection group would include patients undergoing a procedure that has a risk of focal cerebral ischemia such as a coronary artery bypass graft (CABG), in which multiple emboli are believed to occur and lead to the development of cognitive deficits or, less commonly, an obvious stroke. Additionally, patients undergoing carotid endarterectomy and endovascular therapy are at risk for focal ischemic complications and might also benefit from prophylactic neuroprotection. For patients undergoing surgical procedures, a short preprocedure and postprocedure treatment period with a neuroprotective agent that does not adversely affect the procedure...
would be an appropriate consideration (short-term neuroprotection). Second, the long-term neuroprotection group would include people at a high risk for initial stroke because of their underlying risk-factor profile, those who have suffered a transient ischemic attack (TIA), or those who have atrial fibrillation (AF). Patients who have suffered a mild initial stroke are at high risk for recurrence, and secondary prophylactic neuroprotection should also be considered in these patients (long-term neuroprotection). Third, the concomitant neuroprotection group would include those appropriate for prophylactic neuroprotection who are undergoing treatment for an underlying disorder such as hypertension or atherosclerosis. If the drug used to treat the underlying problem also has neuroprotective qualities, patients who develop focal cerebral ischemia during treatment might have limited mortality and morbidity (concomitant neuroprotection).

The development of drugs for the above purposes would entail several steps. Drugs demonstrated to be neuroprotective in acute stroke models can then be given to animals for short or long periods before stroke induction to mimic the clinical trial setting. Both safety and efficacy in improving outcome and reducing deficits can then be assessed. If a drug is safe and effective in animals, safety in humans should then be established over short- and/or long-term periods of testing before efficacy trials are initiated. Efficacy can then be evaluated in a well-designed double-blind, randomized, prospective trial in an appropriately targeted patient population.18

**Short-term Prophylactic Neuroprotection**

Certain invasive procedures are associated with an identifiable, substantial risk for single or multiple cerebrovascular events. Such procedures include CABG, valve replacement, cardiac transplant, carotid endarterectomy, aneurysmectomy, resection of arteriovenous malformations, and endovascular therapy. Patients undergoing these procedures have a defined risk period, and short-term neuroprotection, initiated before the procedure with a neuroprotective agent that does not interfere with the procedure, is attractive.

A diffuse encephalopathy related to multiple small emboli or hypoperfusion is a complication in up to 77% of patients undergoing CABG surgery.19 Obvious focal ischemic deficits causing recognized ischemic stroke syndromes also occur but are less common.20 Although many patients with neuropsychological deficits after CABG improve, some continue to show abnormalities months after surgery. The neuropsychological disturbances after CABG have been related to age and the length of time on bypass.21 The initiation of a neuroprotective agent 1 or 2 weeks before surgery might influence the severity of neuropsychological deficits perioperatively, especially if microemboli are the major contributor to these deficits.22 Ischemic stroke deficits might also be reduced. A study of prophylactic neuroprotection for CABG surgery could be performed by evaluating neuropsychological performance before and several months after surgery in a double-blind, randomized treatment trial. For example, with a sample size of 188 patients who receive active drug or placebo perioperatively (94 per group), a clinical trial could detect a 40% difference of outcome measures on a neuropsychological battery (80% power, α=.05, two-tailed, P<.05). The neuroprotective drugs used for such a trial would have to be devoid of side effects that might affect the surgical procedure, especially hypotension. Preliminary trials with phenytoin and a ganglioside have been performed.23 Although these interventions were ineffective, these studies exemplify the feasibility of performing prophylactic neuroprotective trials in patients undergoing CABG surgery.

With the recently documented efficacy of carotid endarterectomy for TIA patients with high-grade stenosis, the number of these procedures performed will likely increase. Perioperative stroke rates with carotid endarterectomy vary widely but occur in 2.5% to 11% of cases in community hospitals.24 Subgroups of patients undergoing carotid endarterectomy, such as patients with severe contralateral carotid or verteobasilar artery stenosis and patients with mild to moderate residual neurological deficits before surgery, may be at higher risk for perioperative stroke.17,25 Trials of short-term, prophylactic neuroprotection should be considered, especially in high-risk subgroups, which may be better defined as data from the North American Symptomatic Carotid Endarterectomy Trial (NASCET) and the European Carotid Surgery Trial (ECST) are further analyzed. Endovascular procedures, particularly therapeutic embolization of intracranial aneurysms and arteriovenous malformations, are being performed more commonly using a variety of approaches. By the nature of such procedures, the patients undergoing them are at substantial risk for focal ischemic complications.26 Short-term prophylactic neuroprotection is an obvious consideration as an adjunct to therapeutic embolization, and appropriate trials should be considered.

**Long-term Prophylactic Neuroprotection**

It is obvious that for long-term prophylactic neuroprotection to effectively fulfill its promise, the concept must be used in patients at substantial risk for primary or recurrent stroke so that cost and potential side effects can be justified. Several potential patient groups are readily identifiable. Modifiable stroke risk factors such as hypertension, diabetes mellitus, cigarette smoking, excess alcohol use, underlying cardiac disease, and hyperlipidemia have been well documented.27-28 From the Framingham data, Wolf and colleagues29 derived a point system of stroke risk based on the risk-factor profile of an individual patient. Their data suggest that a 10-year stroke probability can be assigned. Applying this approach, patient groups with a high risk for stroke (5% per year or higher) can be identified despite valiant attempts to modify risk factors and reduce stroke risk. For long-term neuroprophylactic trials, a much larger sample size than in short-term trials would have to be followed for at least 3 to 5 years to detect the effects of the drug on functional outcome. Presently, outcome is typically measured in acute stroke treatment trials by the Barthel Index or another activities-of-daily-living scale 3 to 6 months after stroke occurrence. In the Table we provide sample size estimates for long-term neuroprotective trials in patient groups with varying degrees of stroke risk and potential therapeutic benefit. Obviously, long-term prophylactic neuroprotection trials will be much more difficult and costly to perform than...
short-term trials, but the potential benefits also could be commensurate.

Patients with AF, both nonvalvular and valvular, are at high risk for stroke.\textsuperscript{30} It is clear that prophyactic long-term anticoagulation markedly reduces stroke risk in AF patients.\textsuperscript{31} Unfortunately, some patients may not be candidates for anticoagulants because of an underlying medical condition (ie, bleeding disorder, gastric ulcer, etc). Additionally, the risk-benefit ratio for anticoagulation in elderly patients (aged older than 75 years) with nonvalvular AF may be so narrow or nonexistent as to preclude its use in this group at high risk for stroke.\textsuperscript{32} These nonanticoagulated AF patients, who have a stroke risk of 3% to 7% per year, constitute another important group in which prophylactic neuroprotection should be evaluated. AF patients who receive anticoagulants may still have a stroke risk of 2% to 3% per year and may also benefit from prophylactic neuroprotection.

The presence of TIA identifies another population at high risk for stroke. Recent data from the NASCET and ECST unequivocally document that carotid endarterectomy more effectively reduces stroke risk than aspirin in patients with carotid territory TIA who have greater than 70% carotid stenosis.\textsuperscript{33-34} The lower limit of carotid narrowing where surgery remains beneficial has yet to be definitively established. Aspirin and ticlopidine also reduce stroke risk after TIA but only by 20% to 30%.\textsuperscript{35} Therefore, TIA patients who are not surgical candidates might also be appropriate candidates for prophylactic neuroprotection.

Patients who suffer minor or major strokes are at substantial risk for recurrence.\textsuperscript{36} The greatest risk occurs during the first 30 days after ischemic stroke, and there is continued risk among 30-day survivors.\textsuperscript{37} The aggregate risk of stroke recurrence per year has been estimated at 6.1% after minor stroke and 9% after major stroke.\textsuperscript{38} Moreover, there are subgroups with hypertension, elevated glucose on admission, and prior ethanol abuse who may have a particularly elevated risk of stroke recurrence. As the mortality from initial cerebral infarction declines and the life expectancy of the population increases, the number of persons at risk for stroke recurrence will become a greater public health concern. Such patients are typically managed with antiplatelets.\textsuperscript{39} Evaluating prophylactic neuroprotection for these patients would appear appropriate, especially in patients with mild residual deficits who are not endarterectomy or anticoagulation candidates.

Patients with asymptomatic carotid stenosis above 75% have an ipsilateral stroke rate of 2.5% per year and a rate of 3.3% per year in all vascular territories according to the data of Norris et al.\textsuperscript{29} The value of carotid endarterectomy in asymptomatic carotid stenosis is undergoing evaluation, but this population might also benefit from prophylactic neuroprotection.

What pharmacologic approach should be considered in patients who are candidates for primary prophylactic neuroprotection? The drug would have to demonstrate clear evidence of neuroprotection in animal stroke models, have few adverse effects when administered for long periods, and be devoid of interactive effects with other medications used to treat associated medical conditions. Expense will be an important consideration when long-term use of a drug is contemplated, and cost should be in the range of currently prescribed antihypertensive or anticonvulsant medications. Such an ideal drug is not yet available. Several of the neuroprotective drug categories previously discussed contain members that fulfill several of these prerequisites, and medications such as nimodipine, flunarizine, felbamate, demethorphan, and memantine are available and might be considered for prophylactic neuroprotection trials. Other treatments are in various stages of development, and we can anticipate many potential prophylactic neuroprotectants in the near future. An antithrombotic drug with neuroprotective qualities would be particularly attractive for many of the potential treatment populations. Establishing efficacy of prophylactic neuroprotection may be difficult in some long-term treatment subgroups because large numbers of patients will likely have to be studied, and preventive treatments such as endarterectomy, platelet antiaggregants, and anticoagulants may reduce the most important end point of ischemic stroke.
Concomitant Prophylactic Neuroprotection

A third approach to prophylactic neuroprotection is the potential to provide neuroprotection as an ancillary benefit of a medication that is being used to treat another underlying condition associated with stroke risk. Hypertension is likely the most important stroke risk factor, and treating hypertension certainly reduces but does not eliminate stroke risk.28,29 A large variety of antihypertensive drugs are currently available with varying degrees of efficacy and side effects. An antihypertensive drug that also had neuroprotective qualities would certainly be an attractive combination. Such a drug might not only reduce stroke risk by lowering high blood pressure but also reduce ischemic lesion size in those hypertensive patients who suffered a stroke while being treated. Establishing that a drug had such a dual effect might be difficult in clinical trials because of a primary effect of the treatment on ischemic stroke incidence but might be accomplished efficiently in a population at high risk for stroke as defined by the Framingham profile.29 A recently developed β-blocker, carvedilol, is an antihypertensive drug that has both antioxidant and neuroprotective qualities.40,41 This drug exemplifies the concept of therapeutic multiplicity as an approach to concomitant prophylactic neuroprotection.

Patients with moderate to severe atherosclerosis in extracranial and intracranial arteries are at enhanced risk for stroke. Risk factor modification reduces the progression of atherosclerosis, but additional antiatherogenic therapies that intervene at a cellular level in the atherogenic cascade are being developed.42 It is likely that therapies that retard atherosclerotic plaque progression or induce regression will reduce stroke risk, as they have for symptomatic coronary artery disease.43 If such an antiatherogenic agent were also neuroprotective, it would qualify as a candidate for concomitant prophylactic neuroprotection because the drug would offer dual beneficial actions. A voltage-sensitive, antiatherogenic calcium antagonist that also crossed the blood-brain barrier and afforded neuroprotection would offer a mechanism for concomitant prophylactic neuroprotection.

Conclusion

Prevention is a cornerstone of modern medicine and will continue to increase in importance as cost-effective approaches are designed for the 21st century. Pharmacologic advances based on enhanced comprehension of the pathophysiology of focal ischemic brain injury have led to the development of therapies that can potentially ameliorate the consequence of these events. Some of these drugs might be beneficial if given prophylactically in groups of patients with an identifiable high risk for focal ischemic injury. As outlined, prophylactic neuroprotection can be envisioned in many different patient groups with various treatment regimens. Probably the most efficient population in which to initially evaluate the concept of prophylactic neuroprotection is the short-term group. The number of patients required for treatment should be relatively small, the follow-up time short, and the exposure time for the development of side effects modest in comparison with the long-term and concomitant groups. Lessons learned from short-term prophylaxis can then be applied in the longer, more demanding settings.

The development of safe and effective neuroprotective agents that are orally available is under way. The next step is to design and conduct clinical trials in the types of patients discussed and probably others. This concept of prophylactic neuroprotection needs careful evaluation, discussion, and, hopefully, implementation as a novel method to prevent or reduce the consequences of focal ischemic injury in high-risk populations.

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