Duration of Neuroprotective Treatment for Ischemic Stroke

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Background—The therapeutic time window for thrombolysis appears to be extremely short, probably because of the hemorrhagic complications associated with late reperfusion of ischemic brain tissue. Other neuroprotective forms of treatment continue to be developed, although their efficacy has yet to be conclusively proved in patients. The duration of treatment in recent phase 3 trials ranges from a single bolus injection to 12 weeks of oral therapy.

Summary of Review—In this article we discuss the factors that should influence the choice of route and duration of treatment. Excitotoxic injury following stroke evolves over at least 4 hours in rodents and possibly beyond 48 hours in humans. In addition, autoregulation and local cerebral perfusion are deranged for approximately 72 hours in patients with stroke. Neuroprotection should provide cover during this critical time.

Conclusions—Important considerations influencing drug administration should include the pharmacology of the compound (pharmacokinetics, mechanism of action, preclinical toxicity, and pharmaceutical properties), its safety and tolerability in patients, and the likelihood of continuing or recurrent cerebral ischemia, along with practical issues such as ease of administration and interactions with early rehabilitation and other therapies. Optimization of treatment will be possible only when neuroprotection is confirmed to be effective. (Stroke. 1998;29:535-542.)

Key Words: cerebral ischemia ▪ neuroprotection ▪ glutamates ▪ N-methyl-D-aspartate ▪ drug therapy ▪ penumbra

The prognosis for patients with stroke is worse than for many forms of cancer, with half of all patients dead or dependent on others after 1 year. The outcome is even more bleak for patients with severe stroke, with 96% of patients dead or dependent after a total anterior circulatory syndrome. Despite recent encouraging results with rt-PA, there is presently no widely applicable treatment for the majority of patients with acute ischemic stroke. A number of neuroprotective compounds are in advanced stages of clinical development after encouraging results from preclinical studies. There is, however, no consistent approach to dosing schedules for these novel treatments, and as a result, ongoing phase 3 clinical studies of efficacy are using differing and possibly inappropriate durations of drug therapy. In most phase 3 efficacy studies, a drug is administered as soon as possible after stroke, within a predetermined but arbitrary time window. The drug is then often continued for a variable time, depending on the pharmacological properties of the individual compound. For example, studies with tirilazad or selfotel (CGS19755) have restricted recruitment to patients that can be treated within 6 hours. In the case of selfotel, the drug was given as a single intravenous bolus, whereas tirilazad administration was repeated for 72 hours. In contrast, piracetam efficacy was assessed when commenced within 12 hours and continued for up to 12 weeks after the onset of symptoms (Fig 1). It is clear that both in animal models of stroke and in humans, the effects of cerebral ischemia are manifest on the cerebral metabolism rapidly, with a timescale measured in minutes or hours. Any form of potential neuroprotective treatment should therefore be given by the most rapidly effective route, which in practice means intravenously. In an ideal scenario, neuroprotective plasma and central nervous system levels of drugs would be attained immediately. This is widely recognized and is supported by the results of recent thrombolysis trials (NINDS, ECASS, MAST, and MAST-I). and by meta-analysis of nimodipine trial results.

The optimal duration and route of administration of treatment will depend on the individual pharmacokinetic properties of the neuroprotective compound, on the adverse-effect profile of the drug, and on the nature of the insult that gave rise to the stroke. For example, it would be desirable to maintain...
neuroprotection throughout recurrent episodes of cerebral ischemia, ie, recurrent cardiac embolism. While this risk may vary from patient to patient, phase 3 studies should address the safety and efficacy of durations of treatment that are likely to be used subsequently in routine clinical practice.

Pharmacological Properties
Ideally, any compound for the treatment of stroke should adequately cross the blood-brain barrier and obtain sufficiently therapeutic levels within the brain and CSF. Highly lipid-soluble drugs will penetrate the cerebral tissues more rapidly than hydrophilic agents and will also be cleared more slowly from neural tissue. Although scant data are available in human subjects, investigations of the pharmacokinetics of the lipid-soluble neuroprotective agent selfotel in human volunteers suggest that the brain half-life of the drug is significantly longer than the plasma half-life. Selfotel was present in the CSF after 16 hours, in contrast to its plasma half-life of 2 to 3 hours.13 The central nervous system effects were also prolonged: up to 60 hours in patients with stroke. The active drug pool need not necessarily be within the CSF, however, and tissue levels are likely to be more important, as CSF may equilibrate slowly with brain tissue.

Drugs with slow clearance from the brain tissue are more likely to accumulate and lead to toxic side effects if given by constant intravenous infusion but conversely may give prolonged protection if given by single-bolus injection.13 Overall, lipid-soluble agents are more likely to exhibit in vivo activity at relatively lower plasma levels than water-soluble agents, and the drug doses required for neuroprotection may be overestimated by plasma-level calculations and pharmacokinetic modeling. Maintenance doses may not even be required to sustain neuroprotective drug levels within the brain.

At present little is known about the effect of stroke on the integrity of the blood-brain barrier, which is crucial in determining the penetration of less lipophilic compounds. In acute cerebral ischemia it is possible that hydrophilic compounds may cross the blood-brain barrier and thus enter infarcting or ischemic tissue. It is also important to consider the limitations of calculating maintenance drug doses from data based on plasma levels of a drug and/or metabolite, which of course give no indication of CSF and brain levels of the drug during treatment. Studies in which patients are subjected to frequent removal of CSF via lumbar puncture after infusion of neuroprotective agents are unacceptable to most physicians and patients. There are limited data regarding the CSF or brain penetration of these compounds in humans, and thus the quantity of the drug actually reaching the brain is unknown. PET studies using isotope-labeled drugs may give some indication of drug distribution in humans, but there are considerable practical difficulties involved. Patients must be recruited, examined, scanned with CT or MRI, treated, and then subjected to PET scanning, all within several hours of stroke onset.

Binding Properties
At a cellular level the mechanism of action of any particular agent will also determine whether constant exposure to a drug is necessary or indeed desirable. In the case of noncompetitive high-affinity NMDA antagonists such as aptiganel (CNS1102), binding occurs rapidly if the ion channel is open and the drug dissociates slowly.14 Thus, after dosing, increasing numbers of ion channels become blocked over time until steady state is reached. Conversely, lower affinity blockers such as remacemide desglycine will dissociate from the receptor more readily and thus may require a higher loading dose, followed by a maintenance infusion to achieve effective ion channel blockade.

The clearance and volume of distribution of any given compound will influence the doses required but not necessarily the duration of treatment. Where the half-life of a drug is relatively long (eg, as with selfotel), it may be more acceptable to patients and medical staff to give treatment in the form of single or intermittent intravenous bolus rather than a constant intravenous infusion. The exception is in the case of drugs with a narrow therapeutic index, ie, those for which the minimal effective plasma concentration is close to the maximum tolerated plasma concentration. In this case, despite a long half-life,
it may be impossible for patients to tolerate the peak concentrations achieved after each bolus unless doses are so low that the trough concentrations may be ineffective. An example is aptiganel, which in phase 2 studies was given as an initial bolus followed by a constant intravenous infusion, because initial peak concentrations following higher single-bolus injections were associated with intolerable side effects. Tolerability may therefore be improved by minimizing fluctuations in drug concentration. Initial dosing schedules for the glutamate release inhibitor 619C89 used intermittent dosing, whereas more recent studies relied on constant rate infusion.\textsuperscript{15}

Most compounds investigated as possible treatments for stroke in animal models are maximally effective given as initial bolus followed by constant intravenous infusion. The selective competitive NMDA antagonist EAA 090 paradoxically is maximally effective after single intravenous bolus only (P. Danjou, MD, personal communication, 1996). The significance of these differences in humans is unknown and may be marginal or even irrelevant, but they may influence the dosing schedules that are chosen for the evaluation of therapies in future clinical trials.

The therapeutic range, and thus the desirable duration of therapy, is also influenced by the steepness of the dose-response relationship. The effects of aptiganel in healthy volunteers include subjective oral paresthesia and, at higher doses, objective evidence of nystagmus. The dose-response curves differ for these two effects (Fig 2). Which of these effects is more closely related to neuroprotection is unknown, though the paresthesia appears to occur at plasma levels lower than those associated with experimental neuroprotection. If neuroprotection were associated with the paresthesia, frequent or repeated dosing might be unnecessary, because a degree of neuroprotection would persist for many hours after a single bolus dose of aptiganel. Conversely, if neuroprotection were associated with nystagmus, it is likely that plasma concentrations would fall below those required for efficacy within minutes to a few hours after cessation of aptiganel infusion.

Orally active drugs with good bioavailability characteristics may be suitable for longer term postischemia treatment in patients with a high risk of imminent cerebral infarction. It is, however, common clinical practice to withhold food, drink, and oral medications until speech and swallowing have been adequately assessed by a trained speech and language therapist, as swallowing is frequently compromised in patients with recent stroke.\textsuperscript{16} It is therefore likely that early treatment of acute cerebral ischemia will be limited to intravenous drug therapy.

**Mechanisms of Action**

Recent interest has focused on the potential role of the NMDA receptor and EAA in the development of the ischemic penumbra. The EAA glutamate is thought to have a crucial role in the development of neurological damage once cerebral perfusion is reduced to a level at which metabolic activity is compromised but may potentially still recover.\textsuperscript{8} Recovery of perfusion through collateral circulation may lead to a resolution of neurological function, but further neurological damage may result from the subsequent buildup of EAs.\textsuperscript{17–19} Gluta-
mate is the most abundant EAA in the human brain and is normally stored in presynaptic vesicles. Under normal conditions, levels of glutamate are regulated by reuptake mechanisms into neurons and glial cells. Postsynaptic glutamate receptors such as the NMDA, α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA), and kainate receptors are activated as a consequence of increases in glutamate. Activation of these ligand-gated channels leads to the influx of sodium and calcium, which is neurotoxic to the cell. The most conclusive evidence that glutamate-mediated activation of receptors is responsible for expansion of the infarct volume comes from animal models of acute stroke. In these studies, drugs antagonizing the NMDA receptor complex consistently reduce the size of infarction induced by a standardized vascular or hypoxic insult. Potential sites for antagonism of the receptor include the NMDA recognition site that is blocked by selfotel (CGS19755) and 3-(2-carboxy piperazin-4-yl)propyl-1-phospho-D-CPPene; the ion channel that is blocked physiologically by magnesium or pharmacologically by aptiganel and dizocilpine (MK-801); and the glycine site, because glycine binding is required for the activation of the receptor blocked by GV150526 and ACEA1021. Clinical studies are currently underway to assess tolerance and efficacy of these drugs in patients with stroke. In addition, a polyamine site distinct from the ion channel but part of the NMDA receptor complex (possibly the NR2B subunit) has been identified, and antagonists are currently in clinical development. GABA-A receptors have important inhibitory functions within the central nervous system, and a number of agonists have been assessed in models of focal ischemia. GABA administration blocks the excitotoxic effects of glutamate, including depolarization and calcium influx. GABA-mimetic drugs, such as clomethiazole or muscimol, are neuroprotective in animal models, and combination therapy with NMDA antagonists (eg, MK-801) may be more effective, but GABA agonists are associated with a high incidence of respiratory depression. Like the NMDA antagonists, they act on membrane receptors and should be administered within the same time window and over the same period.

Free radicals are thought to have a role in mediating ischemic neuronal damage and, in particular, reperfusion injury. The combination of ischemia, a rich supply of metal complexes (eg, iron from hemoglobin), and a paucity of free radical neutralizing enzymes (superoxide dismutase, catalase, and glutathione peroxidase) within the brain predisposes to neuronal damage mediated by free radicals. The synthetic 21-amino-steroid tirilazad has free radical scavenging activity, analogous to that of vitamin E. It also has antioxidant effects, inhibiting the generation of hydrogen peroxide and blocking the release of arachidonic acid from injured cell membranes. It is effective in animal models of stroke, reducing the volume of infarction in the rat MCA occlusion model, but so far phase 3 clinical trials have been inconclusive. Enzymes such as superoxide dismutase can convert unstable free radicals to more stable, less harmful molecules. Unfortunately, these do not directly cross the blood-brain barrier, but conjugation to lipid-soluble agents (eg, polyethylene glycol) may allow blood-brain barrier penetration. These mechanisms are currently undergoing preclinical evaluation. These drugs have the potential to be given later than other neuroprotectives, as reperfusion may occur many hours or days after stroke.

Neutrophils also have a role in the development and maturation of cerebral infarction and mediate some aspects of reperfusion injury. Neutrophil adhesion is mediated by specific adhesion molecules that are essential in initiating the release of cytotoxins and controlling cellular activation. Monoclonal antibodies to these adhesion molecules (ie, anti-CD11 and anti-CD18) also reduce infarction volume but are unsuitable for clinical use because of their immunogenicity. A recent study has shown the effectiveness of a recombinant neutrophil inhibitory factor derived from hookworms in reducing infarct volume after MCA occlusion in rats. This correlated with a reduction in the number of neutrophils found within the infarcted tissue. It is possible that immunologic therapies will also have a broader window of opportunity, because they modulate more delayed effects of infarction. Studies have evaluated treatment following 2 hours of middle cerebral artery occlusion in rats. Further studies should evaluate the possibility of significant neuroprotection beyond the time window already established for NMDA antagonists in animal models.

It is likely that the lack of efficacy of thrombolysis beyond 3 hours results at least in part from reperfusion injury. Because both free radical scavengers and leukocyte adhesion inhibitors may reduce reperfusion injury, they should be considered possible adjuvant therapy in combination with thrombolytic treatment. Reperfusion promoted by thrombolytic drugs probably occurs within at most a few hours of drug administration and spontaneous reperfusion up to a few days after occlusive stroke. If combination therapy with a neuroprotective agent and a thrombolytic drug is contemplated, it should be sufficient to administer the drugs together and to maintain treatment with the neuroprotective agent for 2 to 3 days.

**Side Effect Profiles and Safety**

While it may be appropriate in some cases for neuroprotective therapy to be continued for hours, days, or even weeks after acute ischemic insult, a paramount consideration is the tolerability and patient acceptance of any potential therapy. A number of neuroprotective agents have already been shown to have dose- and duration-limiting side-effect profiles. In particular, the more potent NMDA antagonists are associated with severe psychotomimetic effects. Aptiganel may cause light-headedness, dizziness, paresthesia, sedation, and even paranoia; selfotel has been associated with agitation, confusion, headedness, dizziness, paresthesia, sedation, and even paranoia; and anti-CD18) also reduce infarction volume but are unsuitable for clinical use because of their immunogenicity. A recent study has shown the effectiveness of a recombinant neutrophil inhibitory factor derived from hookworms in reducing infarct volume after MCA occlusion in rats. Further studies should evaluate the possibility of significant neuroprotection beyond the time window already established for NMDA antagonists in animal models.

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Drugs that block the glycine site of the NMDA receptor appear as effective as other NMDA antagonists in reducing neurological deficits in animal models of acute stroke. Clinical and volunteer studies with the glycine antagonist GV150526 suggest that it is extremely well tolerated and compares favorably with other compounds under investigation (A.G.D., K.R.L., unpublished data, 1996). Magnesium may also block the influx of calcium into ischemic neurons and has been shown to be neuroprotective in animal models. It is cheap to produce and appears to be well tolerated in initial pilot studies in patients. Magnesium has also been tested in over 50,000 patients after acute myocardial infarction, without ill effects. Although the Intravenous Magnesium Efficacy in Stroke (IMAGES) study will be using only a 24-hour infusion requires further clarification.

Hemodynamic Effects
A further concern is the potential hemodynamic effects of these agents, particularly on BP. In acute stroke, cerebral autoregulation is lost and local cerebral perfusion becomes dependent on systemic blood pressure. Changes in BP may increase or reduce local cerebral blood flow. Dose-dependent increases in blood pressure are seen with the NMDA antagonist aptiganel, with rises of mean arterial blood pressure up to 30 mm Hg. This has not been shown to affect total cerebral blood flow, but MCA velocity is increased. At present it is not known whether the cerebral hemodynamic changes are reproduced (or clinically relevant) in stroke patients. It is conceivable that rises in systemic blood pressure could lead to exacerbation of cerebral edema or even hemorrhagic transformation of infarction, but it is equally possible that more prolonged infusions could be given to patients. Thus, the tolerability of any potential treatment for stroke will determine its suitability for prolonged administration.

Neuronal Vacuolation
Evidence from animal models of stroke suggests that after an ischemic insult, neurological damage spreads out circumferentially from the central core of the infarct. If ischemia is present for over an hour, the volume of the infarct gradually enlarges to its maximal size over a period of 3 to 4 hours in rodents and 6 to 8 hours in nonhuman primates. PET scanning can differentiate between ischemic and infarcted tissue, and evidence from studies in humans suggests this time window may even extend to more than 48 hours in patients with stroke. The phase of misery perfusion, ie, locally reduced flow, is present in 100% of patients scanned within 9 hours and drops to 30% within 4 days, with ischemic but viable tissue demonstrated for up to 48 hours after onset of stroke. There is consequently

Figure 3. A, Blood pressure changes vs time in days after stroke in patients receiving placebo, 1 mg/h, and 2 mg/h IV nimodipine. B, Patient outcome score vs time in weeks in same groups. Results show dose-dependent reduction in Barthel Index score (poorer outcome) in the nimodipine treatment group, correlating with reduction in blood pressure.
a rationale for initiating and continuing neuroprotective treatment up to at least 48 hours after stroke onset.

Because regional blood flow abnormalities tend to resolve in most cases after 3 to 4 days, it is likely that these areas are reperfused via collateral vessels which develop in the intervening time. At this time cerebral autoregulation is deranged and as a result is unable to maintain constant perfusion levels in the face of fluctuating systemic BP (Fig 4). There is at present no investigative procedure (including PET scanning) that allows clinicians to predict accurately which areas of ischemia will recover and which will progress to infarction. In the latter case, collateralization may simply lead to reperfusion injury. Observations in a single patient after a large ischemic stroke suggest that EAAs remain grossly elevated for at least 6 days after stroke.46 These data were gathered with a microdialysis probe inserted into an area of infarcted tissue during a neurosurgical procedure to relieve the raised intracranial pressure that followed a large cerebral infarct. The conditions of the study were therefore not typical of the patients presenting with acute ischemic stroke. It would seem logical to protect patients during the time the collateral circulation is developing and cerebral autoregulation is deranged (ie, for 3 to 4 days after onset), but if this case report accurately reflects the time course of EAA elevation after stroke, there may be a rationale for more prolonged administration (ie, 6 to 7 days).

**Prolonged Therapy for Certain Patients?**
The risk of further cerebral ischemia after stroke or TIA is highest immediately after the initial event. Results from the Oxford Community Stroke Project suggest that the absolute risk of a further cerebral ischemic episode is 4.4% during the first month and 8.8% in the first 2 months. The odds ratio of a stroke in these patients compared with age-matched controls without recent symptoms of cerebral ischemia is 80.0 within the first month and 27.0 within the second. Thereafter, the odds ratio diminishes to 4.7 between 1 and 2 years.48 While the risk of further stroke is relatively high in these patients, extrapolation of these results suggests that between 50 and 100 patients would require treatment for 1 week (or, alternatively, 25 patients for 1 month) to provide neuroprotection during a single recurrent event.

Patients with high-grade stenosis of the internal carotid artery who are awaiting endarterectomy have a significantly higher risk of further recurrent stroke. In the control arm of the North American Symptomatic Carotid Endarterectomy (NASCET) trial, the risk of stroke over a 2-year period in patients with high-grade ulcerative lesions was 30%.50 The risk of recurrent brain embolism in the 14 days following cardioembolic stroke has been reported to be 13.7%, with the highest risk found in the 2 days immediately after the stroke.51 There are, therefore, subgroups of patients who can be identified as being at higher-than-average risk of further ischemic events and who potentially could benefit from longer-term neuroprotection. For prolonged treatment to be practicable it would ideally be available in an orally active form and have an acceptable side-effect profile. Drugs could be given over a period of several days through the intravenous route, since anticoagulants are frequently administered in this way after a thromboembolic event. However, potential interactions with drugs commonly used in the management of stroke patients, such as warfarin and aspirin, would have to be assessed.

**Practical Issues of Administration**
For neuroprotective treatment to be effective, patients will likely require initiation of therapy within, at most, 12 hours after the onset of symptoms. Thus, the healthcare infrastructure must facilitate the rapid referral, transfer to hospital, emergency assessment, and treatment of such patients. Until now, with no proven therapy available for acute stroke, referral practices and assessment times have been extremely variable, both internationally and locally. The recent results with rt-PA are unlikely to change this situation, but should neuroprotection be demonstrated to be effective, it is likely that this would improve, possibly with the development of a fast-track referral system analogous to that in operation for patients with suspected myocardial infarction. It is conceivable that general medical practitioners or even paramedical staff members could give an initial bolus dose of treatment before hospital transfer. Preparations of such drugs would need to be easy to administer and safe in patients with intracerebral hemorrhage, as clinical signs are unreliable in the diagnosis of this condition.52 The same caveat would apply to any form of therapy being considered for use in smaller hospitals and isolated communities in which there is no access to CT scanning facilities.

**Potential Problems**
When considering how long intravenous treatment may be continued, the potential effect on patient rehabilitation should be considered. Patients receiving intravenous infusions are often immobilized as a consequence, and this in itself may
reduce the effectiveness of early attempts at rehabilitation. Furthermore, any treatment that immobilizes patients after stroke is likely to lead to an increased risk of thromboembolic complications, such as deep venous thrombosis. Prolonged infusions are associated with a risk of local phlebitis, and indeed several agents under development are locally irritant. It would therefore be ideal if treatment could be administered initially in an intravenous preparation and later converted to an oral formulation as soon as the patient is mobilized. Drugs with potential respiratory depressant or sedative effects, such as the AMPA antagonists, may cause practical problems in the management of stroke patients, in addition to increasing the risk of complicating aspiration pneumonia. It may be impossible to distinguish between the sedation caused by a complication of the initial stroke (eg, secondary hemorrhage leading to raised intracranial pressure) and the sedation induced by the neuroprotective drug. Whenever possible, appropriate concentrations of a drug should be prepared in order to avoid fluid overload. Short-term administration of high fluid loads (eg, 500 mL in 1 hour) may be safe or even desirable in a dehydrated patient but may precipitate heart failure in others.

Conclusions

In summary, it is hoped that ongoing clinical trials will demonstrate the efficacy of neuroprotective therapy in patients with acute stroke. When trials are conceived, it is important to consider the way in which these drugs are likely to be used by physicians in the future and to design trials accordingly. Side-effect profiles of these agents are crucial to the way in which drugs may be prescribed; for example, agents with potent adverse side effects (ie, psychotomimetic effects) may be suitable only for a single bolus or short-term infusion. With well-tolerated preparations, the optimal duration of treatment is probably at least 72 hours, ensuring neuroprotection while cerebral hemodynamics are compromised. New evidence, however, suggests that EAAs may be grossly elevated for at least 6 days after large ischemic strokes, suggesting a possible rationale for more prolonged acute therapy. Drugs may be combined in the future in such a way that potent drugs with potentially upsetting side effects are given as an initial bolus, with a better-tolerated preparation used for prolonged therapy. Reperfusion injury may be reduced by administration of free radical scavengers or immunologic modulators that reduce the influx and adherence of leukocytes in the infarct zone. Additional neuroprotection for high-risk patients may continue if a suitable, well-tolerated, orally active therapy is available. Ideally, acute therapy would be available for administration by nonprofessional medical and paramedical staff members, as this would facilitate the earliest possible initiation of neuroprotection. Interactions of these agents with drugs frequently given to patients with acute stroke will require assessment. Finally, the relation between acute changes in BP and stroke outcome requires further attention, because some of these agents are likely to have hemodynamically significant effects.

References


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