Acute Stroke Therapy Trials: An Introduction to Recurring Design Issues

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We discuss selected issues concerning the design of stroke treatment trials. Key issues include the type of stroke studied, the time interval from stroke onset to patient entry, and whether to include cardioembolic strokes and allow concomitant therapy. (Stroke 1987;18:524-527)

Despite the fact that stroke is a major cause of death, disability, and economic loss, clinicians continue to debate how they should treat acute stroke patients, or even if they should use any specific treatment at all. One major reason for this controversy is that the most widely used treatments are of unproven benefit and have not been subjected to adequate controlled studies.1 Because we are entering a period when rapidly increasing knowledge of stroke pathophysiology forecasts new therapeutic approaches, it becomes especially important that potential therapies be studied according to rigorous, well designed clinical trials.

There are several important reasons why it is especially difficult to design therapeutic trials for acute stroke. Knowledge is incomplete regarding the pathologic and cellular events that lead to cerebral infarction or that contribute to the still-reversible brain dysfunction in the ischemic penumbra.2 3 Although some of these events have been identified, they are complex and diverse, including alterations in local blood flow, energy metabolism, and tissue pH, tissue edema, transmitter release and neuronal activation, membrane damage with production of arachidonic acid, calcium flux, and other changes that act alone or in combination to disrupt neuronal structure and function.

The precise molecular events, their timing, and their interplay are largely unexplored. In addition, when a patient presents with a stroke syndrome, important characteristics of the ischemic event generally cannot be immediately determined, e.g., its duration and future course, the precise cause, and the site and degree of arterial obstruction. Acute stroke therapy trials that attempt to address this complex scenario with poorly designed study plans are likely to produce incomplete or meaningless results despite much cost and labor. Such complexities have even caused some to question whether acute stroke therapy trials can be done at all.

General Considerations

In designing stroke studies two cardinal but potentially conflicting requirements must be satisfied: the entry criteria must be adequately liberal to allow reasonable patient recruitment, but must also be sufficiently restrictive to ensure appropriate patient homogeneity. Ethical and safety issues also need to be considered. As much as possible, eligibility criteria should be guided by the principle of identifying patients who are most likely to benefit from the proposed treatment.4 For instance, a drug that putatively acts exclusively on cellular acidosis may not be effective in treating patients who have an intracerebral hematoma; alternatively, an agent putatively minimizing massive cerebral edema might not be effective in treating a small lacunar stroke.

In determining patient eligibility a general approach defines the patient population by using inclusion and exclusion criteria.4 These criteria, central to the design of the studies, include several key considerations: 1) assuring a sufficiently homogeneous patient population determined as much as possible by the knowledge of disease pathophysiology, 2) designing protocols that will detect and quantify changes (either improvements or deteriorations) in the patient’s condition, 3) excluding patients who are at high risk for adverse effects, e.g., pregnant women, 4) ensuring that patients are otherwise as healthy as possible so that they can complete the course of the study (except if death itself is the response variable), and 5) including patients capable of and willing to cooperate with the study requirements.

One approach to eligibility uses inclusion criteria to define the most vital and essential patient characteristics; for instance, establishing whether the study population will consist of patients with subarachnoid hemorrhages, lacunar infarcts, hemispheric strokes, etc.
Pathoanatomic Considerations

In studies designed to evaluate treatments of acute ischemic infarction, there are several advantages to studying patients with hemispheric lesions. As a practical point, infarction in this location occurs with sufficient frequency to allow adequate patient entry. Importantly, for rating clinical status, infarctions in the middle cerebral artery distribution give the investigator reasonably objective criteria (e.g., motor deficits). While brainstem strokes may also provide quantifiable signs, several lines of evidence suggest that they should not be routinely included in stroke treatment trials. The natural history of brainstem infarction probably differs from hemispheric stroke. Also, while the motor deficit accompanying a brainstem infarct is quantifiable by bedside and functional evaluation, other aspects of brainstem lesions, such as the degree of dysarthria, magnitude of tremor, or degree of nystagmus, require special examinations. This range of dysfunction makes data analysis potentially more complicated by introducing response variables that are more difficult to quantify.

Among patients with hemispheric infarcts, investigators need to consider two special situations. The first of these is massive hemispheric destruction with attendant cerebral edema, altered consciousness, and brainstem compression. This situation may introduce considerable variability into a study population. These massive lesions have poor prognoses, and the high mortality rates reduce the number of patients available for functional evaluation. In addition, because of extremely severe brain damage, such patients may no longer respond to many potential therapies that might be effective in less severe ischemia. However, certain therapies (e.g., antiedema) might be most effective in this subgroup, and death may be an appropriate response variable. Finally, severe neurologic dysfunction such as coma or dense hemiplegia may hinder the ability to detect changes; for instance, patients with impaired consciousness will be unable to cooperate with the neurologic examination.

A second group of patients that deserves special consideration is the group with progressing stroke. Clinically, we often cannot separate acute stable infarcts from progressing lesions (especially in many patients who are seen early), and pathophysiologic characterization is not possible with current technology. Patients with stroke in rapid evolution can introduce unwanted variability into a clinical trial because of the difficulty in predicting how far the damage will advance before stabilizing or whether it will progress to a completed hemispheric infarction with the associated high mortality risk and other special problems. Study design should consider the putative mechanism of action of an experimental compound, i.e., does the modality act by reversing and/or preventing progression of the ischemic process, and it should provide an operational definition of stroke in evolution.

Lastly, the site of arterial occlusion should be considered. Broadly speaking, lacunar infarcts due to arteriole-level occlusive disease should be separated from infarcts due to large vessel disease. However, this distinction is often imprecise, based on early clinical findings in the absence of angiographic data.

Entry-Time Considerations

In determining the most appropriate time interval between the onset of the stroke symptoms and a patient's entry into the clinical trial (e.g., first dose of an experimental drug) the experimental design must reconcile two potentially conflicting needs. This interval must be sufficient to allow an effective rate of patient enlistment but not so long as to risk missing the optimal time for therapeutic intervention. In approaching the important entry-time question, study designers must consider issues including practical concerns, pathogenetic mechanisms, clinical trial data, and the possibility of failing to detect a therapeutic effect.

In terms of practical considerations, the recent Scandinavian multicenter study demonstrated that the greatest loss of potential entrants was the inability to admit patients within the 48 hours required, a finding similar to that of Alter (M. Alter, personal communication). It is a practical reality that patients are often delayed in obtaining medical care after the onset of stroke symptoms. Data from the National Survey of Stroke demonstrated that only about 60–65% of patients with infarctions (ischemic and embolic) are admitted to a hospital within 1 day of the onset of their stroke, a figure which rises to about 75–80% by the second day. These data show the time required to arrive at a hospital, but they do not address the additional period necessary to complete baseline evaluations (computed tomography scan, laboratory tests, informed consent, assuring patient and family support, etc.).

Delays from stroke onset to hospital admission may be most pronounced at those academic medical centers best prepared to participate in multicenter clinical trials. For example, patients referred to tertiary academic centers often arrive from smaller community hospitals; inner-city academic centers may experience delays during the admission process or from the need to provide medical treatment. Researchers should consider the practical point that clinical trials which enter patients with 24–48 hours after the stroke duplicate the realistic clinical situation. Thus, delays of up to 48 hours would include most of the patients seeking medical help after a stroke. Novel ways to shorten entry time, such as deferred consent, should be considered. Investigators also need to realize that very short entry periods will admit many patients with transient ischemic attacks (TIAs), thus introducing considerable heterogeneity into outcome data.

In terms of the pathogenesis of ischemic damage, an
entry time of 48 hours might be a reasonable compromise for many types of therapy. The concept of an ischemic penumbra, an area of jeopardized and malfunctioning but still viable brain surrounding a zone of dead tissue, implies the possibility of therapeutic intervention. Recent research suggests that multiple, interactive events determine the fate of the ischemic penumbra. These events include release of neurotransmitters, lipolysis, changes in protein metabolism and structure, edema, alterations in microcirculation, changes in local pH, and injury to axons of passage. Knowledge of the time course of individual events and their cascading interactions is extremely incomplete, but some may develop during many hours or a few days. For example, experimental data show that under certain conditions neuronal necrosis does not appear for many hours or several days after an acute ischemic injury. As we learn more about the timing of specific postischemic events, investigators will be better able to adjust entry time to the proposed mechanism of the therapeutic intervention.

Spence and Donner's landmark review of issues in the design of stroke treatment trials included a review of trials that had been done up to that time. Patients were admitted into those trials from 24 to 96 hours after the onset of stroke. More recent studies, however, have admitted patients up to 48 hours after ischemic stroke. While it is probably desirable to start therapy as early as possible after establishing the diagnosis, data from clinical trials can be analyzed to determine the impact of the entry time variable on eventual outcome (although this would require a sufficiently large number of patients).

Cardioembolic Stroke: Atrial Fibrillation and Valvular Heart Disease

In considering whether or not acute stroke trials should include patients with valvular heart disease and atrial fibrillation, patients who presumably have had cardioembolic strokes, there are practical, diagnostic, and pathogenetic issues. Practically, recent reviews show that cardioembolic strokes may comprise up to 30% (depending on classification scheme) of all infarcts. Thus, a decision to exclude cardioembolic strokes would eliminate a considerable number of potential patients.

A prerequisite for decisions on admitting patients with cardioembolic stroke (or any other stroke subtype) is that clinicians can establish this diagnosis with reasonable accuracy. Unfortunately there are no universally accepted diagnostic criteria for cardioembolic stroke, and the incidence of this subtype has varied widely in different surveys, from only 13% to nearly 30% of all strokes. Data from the National Survey indicate that only 28% of diagnosed embolic infarctions of the brain are considered "definite."

While atrial fibrillation and valvular heart disease are considered important criteria for the diagnosis of cardioembolic stroke, these conditions may also cause strokes through mechanisms other than embolism. For instance, nonvalvular atrial fibrillation might cause brain ischemia by low cardiac output coexisting with atherosclerosis of the carotid arteries. Atrial fibrillation may simply be a marker of cardiocerebrovascular disease.

Individual stroke treatment trials may have specific reasons for including or excluding patients with cardioembolic stroke, but this diagnosis then requires a clear operational definition. In the trial of a particular therapy, investigators need to consider whether it makes a difference if emboli arise from the carotid artery or the heart; in both cases neurons distal to an obstructed vessel experience ischemia. In trials designed to modify intraneuronal molecular events of "the final common ischemic pathway," investigators should consider admitting patients with strokes caused by different mechanisms since the target of the study treatment is presumably independent of the precise etiology. For instance, an agent stabilizing neuronal membranes might be effective in treating strokes caused by several different mechanisms (i.e., thrombosis, embolization, or low flow), but a thrombolytic treatment would presumably require the presence of a fresh arterial thrombus.

Concomitant Therapy

Even though there is no scientifically established therapy for acute stroke, the issue of concomitant therapy is often raised during the design of acute intervention trials. Most often debated is whether or not anticoagulation with heparin should be allowed, especially in patients with presumed cardioembolism or large-vessel, high-grade stenosis. It is both possible and desirable to design scientifically valid multimodal therapy trials. For example, the factorial design permits an analysis of two separate therapies while requiring only a slightly larger sample size than that required for a single therapy. It is entirely possible that unimodal trials will not demonstrate efficacy since many are designed to detect a large therapeutic effect from one agent acting on only a small part of a complex process. This danger is even more apparent considering the high false-negative rate (Type II error) inherent in most current stroke therapy trials due to inadequate sample size.

An important practical concern in determining whether or not patients in stroke trials should receive concomitant therapy is the reality that many will already be taking aspirin. Many stroke-prone individuals are likely to be taking aspirin for coexisting heart disease or previous TIAs. Because patients in the stroke-prone age group are older than the general population, they have a relatively high incidence of joint diseases, often treated with anti-inflammatory–antiplalet agents.

Personal bias as well as ethical concerns often make it difficult for a clinician to withhold concomitant therapy. For example, if a physician believes that a patient's stroke was caused by cardiac embolism and that there is danger of more emboli, it may be ethically difficult to withhold anticoagulant treatment. Similarly, if evidence that aspirin prevents new strokes in-
creases, it will become difficult to withhold this treatment in patients with acute events.

In determining whether or not patients in clinical trials of another agent might receive treatment with anticoagulant or antiplatelet drugs (or any other concomitant therapy) several pharmacologic points need to be addressed. A chief concern is whether an experimental drug therapy itself putatively acts by an antiplatelet or anticoagulant action or by an unrelated mechanism. In the latter case, it may be no more logical to withhold antiplatelet drugs than it would be to withhold drugs necessary to treat coexisting hypertension, heart failure, cardiac arrhythmias, or diabetes, all of which, if untreated, could greatly affect the prognosis. If an experimental therapy putatively acts on the final common cellular and molecular pathways of the ischemic process, then concomitant treatment aimed at the primary etiology (e.g., thrombosis), if uniformly applied in the study, would reduce variability by preventing additional ischemic damage and may well have an additional beneficial effect.

Length-of-Stay Considerations

A relatively new concern in the design of stroke studies is that even moderate increases in inpatient hospitalization may be extremely costly and financially unacceptable to hospital administrators. Therefore, depending on the safety record of the experimental therapy, studies must be prepared either to provide financing for continued inpatient stay or to permit outpatient follow-up. Thus, a vital eligibility requirement might be a patient’s capability of returning for scheduled outpatient visits, taking the drug regularly, and returning for unscheduled appointments as needed.

Conclusions

Improperly designed or executed acute stroke trials virtually assure future therapeutic uncertainty. Even well designed studies are difficult or impossible to compare if they use varied entry criteria, divergent clinical designs, or very different response variables. Hence, a certain amount of standardization is desirable.

This article provides an overview of selected aspects in the design of acute stroke therapy trials. Special topics, including vital statistical issues, concomitant therapy, rating scales, and response variables will be the subject of subsequent, more detailed reviews. It is essential to consider these topics in study design, but they are beyond the scope of this overview. We recognize that a particular study oriented toward modifying a specific putative cellular event may have different design requirements than another study oriented toward changing other cellular processes. Nonetheless, we wish to develop a flexible framework that best addresses the question, “Does this therapy improve outcome in patients with acute brain infarction?” It is our hope that our comments will engender further discussion and ultimately consensus within the cerebrovascular research community about certain recurring issues in the design of acute stroke therapy trials.

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