

## Ethical Challenges in Stroke Research

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**Background**—Ethical issues are a critical consideration in the design and conduct of clinical research.

**Summary of Review**—A number of completed trials of proposed stroke treatments raise classical ethical issues in challenging ways. The combination of acutely ill and vulnerable patients, the use of potentially toxic drugs, and very short time frames for decision making and drug administration demand an especially careful evaluation of risk and benefit, the process of consent, and the permissible treatment of control patients.

**Conclusions**—The study of acute stroke treatments may require more complex safeguards than other neuroclinical trials. (*Stroke*. 1998;29:1725-1729.)

**Key Words:** clinical trials ■ ethics, medical ■ informed consent

In the past decade, clinical research into potential treatments for acute stroke has dramatically increased. With the support of the NINDS and the National Stroke Association, the watchword has been “acceleration”—both of the involvement of patients in studies and of the research enterprise itself.<sup>1,2</sup> Although the translation of animal experiments into human trials has, in some cases, been criticized as ill conceived,<sup>3,4</sup> this has been a relatively minor voice in a chorus of enthusiasm.

As stroke trials have been designed, reviewed, and implemented, all of the classic ethical issues—risk, benefit, consent—have required attention. Alves and Macciocchi<sup>5</sup> have recently reviewed these issues as they apply to neuroclinical trials in general. Yet many stroke trials, bringing together combinations of acutely disabled and vulnerable patients, potentially toxic drugs, and very short time frames for decision making, pose questions that have yet to receive a thorough airing.

In this article I will discuss two studies that raise challenging issues of risk-benefit, consent, and the treatment of patients in control groups. I will suggest that particular attention be paid to the ethical importance of the timing of treatment and the ability of acute stroke patients to give valid consent to participation in clinical research.

### Thrombolysis and the Treatment of Control Groups

In December 1995, the groundbreaking NINDS study<sup>6</sup> reported that rtPA can reduce long-term disability from acute ischemic stroke with an acceptable margin of safety when given to carefully selected patients within the first 3 hours of the onset of symptoms. Because pilot studies had suggested that patients with severe hypertension would be at increased risk of cerebral hemorrhage with rtPA, potential enrollees

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who were severely hypertensive were treated with “nonaggressive” measures, such as intravenous boluses of labetalol and/or nitroglycerin paste, to try to reduce their BP to an acceptable range—below 185 systolic and 110 diastolic.<sup>7</sup> Once patients had been enrolled and randomized to rtPA or placebo, their blood pressures were closely monitored, and because it was a double-blind study, antihypertensive treatment was given to patients in either group if pressure exceeded the threshold of 180/105. Treatment options included intravenous sodium nitroprusside, intravenous labetalol, or oral or sublingual nifedipine. During and after treatment patients were to be observed for hypotension.

Ethical questions arise around both the lowering of BP to facilitate enrollment and the subsequent treatment of BP in both control and rtPA patients whose BP exceeded 180 to 185/105–110. If, as I believe, reducing BP so soon after presentation, and at this threshold, was contrary to commonly recommended management and carried at least a theoretical risk of harm (see below), this intervention breached the venerable maxim “primum non nocere”: first, do no harm. While those who ultimately received rtPA stood to gain something critical if their risk of hemorrhage was diminished, there was no proposed medical rationale for treating the control group in this way. Urgent BP reduction offered the subjects in the placebo arm no benefit that would make a risk of hypotension worth taking. Furthermore, exposing control patients to this unconventional and potentially risky intervention denied them what control patients should receive (optimal standard treatment), and by doing this created potential doubts about the study’s conclusion that rtPA is superior to best current medical management.

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**Selected Abbreviations and Acronyms**

BP	= blood pressure
IRB	= institutional review board
MAP	= mean arterial pressure
NINDS	= National Institute of Neurological Disorders and Stroke
NMDA	= <i>N</i> -methyl-D-aspartate
rtPA	= recombinant tissue-type plasminogen activator

The issue of if, and when, to treat elevated BP in the setting of acute stroke has been debated for decades.<sup>8,9</sup> Many experts have advised that even very severe hypertension not be treated without an additional medical justification,<sup>8,10</sup> while proponents of treatment have advised caution and have set targets at or above the levels treated in this study.<sup>11,12</sup>

The rationales for restraint in the setting of acute stroke are many and well known: (1) the tendency for hypertension to self-correct,<sup>13</sup> (2) the elevation of the autoregulatory threshold in many stroke patients and the loss of autoregulation in the ischemic area,<sup>14</sup> (3) the need to maintain perfusion of at-risk (penumbral) tissue,<sup>15</sup> (4) reports of patients with cerebrovascular symptoms that worsened with BP reductions very close to this study's intervention point,<sup>16–18</sup> and (5) evidence that reduction of MAP exceeding 13% to 16% can impair cerebral perfusion without producing any clinical signs of deterioration.<sup>19,20</sup> Supporting the traditional caution about blood pressure, two recently published therapeutic trials<sup>21,22</sup> have suggested an association of worsened outcomes with rather modest BP reductions in acute stroke patients.

Restricting BP treatment to “nonaggressive” measures in the NINDS study was clearly intended to safeguard those receiving rtPA while minimizing the risk of harm to the placebo group. However, it was not possible to know in any given patient that BP reduction would not impair cerebral perfusion to some degree and thereby worsen outcome. Labetalol in the recommended doses has been reported in a few cases to reduce BP more than the critical 13% to 16%,<sup>23,24</sup> and there are many cases reported of abrupt hypotension with sublingual nifedipine.<sup>25</sup> While those in the rtPA group might have been protected from any adverse effects of BP reduction had reperfusion been established, no such benefit would have been expected for those in the control group.

Whether the treatment of blood pressure actually harmed patients or skewed the study's conclusions cannot be gauged without knowing, at the very least, whether many or few were treated and whether their outcomes were different than those whose BP did not require intervention. Aside from this methodological question, there are, in my view, ethical problems with the otherwise unjustified reduction of BP to recruit experimental subjects and the further treatment of the control group with this potentially risky intervention without a compelling medical rationale.

The issue of what risks one may expose control patients to has also arisen in studies of intra-arterial thrombolysis. Such treatment has required angiography to identify an occluded artery, to administer the drug directly into this vessel, and then to evaluate the effect of the treatment on the occlusion. While some have suggested that the performance of angiog-

raphy and sham treatment for the control arm of such studies would expose these patients to unconventional risks without commensurate benefit,<sup>26</sup> others have written that this would be acceptable if consent were obtained.<sup>27</sup> Although this issue seems as yet unresolved, at least one such study has already been reported<sup>28</sup> and another is in the planning stages.<sup>29</sup>

**The Timing of Neuroprotective Drugs**

The excitotoxicity theory of cell death in acute cerebral ischemia has focused attention on glutamate as a potent neurotoxin. The finding that NMDA antagonists could reduce glutamate-induced cell death in tissue culture led to the testing of a number of candidate agents in animal models of stroke.<sup>30,31</sup> Although concerns existed about possible neuronal injury induced by NMDA antagonists, it appeared time to proceed to human phase 1 trials when several animal studies reported encouraging results if the drugs were given within 2 to 3 hours after stroke onset.<sup>31–33</sup> By the early 1990s there were some data on the effects of dextrorphan, and the closely related dextromethorphan, in humans at therapeutic doses, and there was substantial reason to anticipate that when given to stroke patients, there would be psychotomimetic and vestibular side effects,<sup>33–35</sup> if not hypotension or respiratory depression.<sup>30,36</sup> Nevertheless, it was hoped that the neuroprotective benefit would outweigh any short-term, reversible adverse effects.<sup>37</sup>

In a multicenter study of safety, tolerability, and pharmacokinetics, 51 acute stroke patients received dextrorphan up to 48 hours after the onset of stroke.<sup>38,39</sup> To be eligible, patients had to be alert, neurologically stable, and without a significant psychiatric disorder. Their baseline National Institutes of Health Stroke Scale scores ranged from 1 to 20.

All subjects had “adverse events.” A quarter of the patients vomited, more than one third experienced dizziness or nausea, and over 50% suffered somnolence, agitation, hallucinations, and/or confusion. These latter symptoms were especially frequent during 11-hour continuous infusions of the drug. Seven of 21 patients receiving the highest loading doses had symptomatic blood pressure drops (in 6 patients exceeding 50 mm Hg). Another patient became hypotensive after treatment of hypertension, which was likely a consequence of drug-induced agitation. At the highest maintenance infusion rate, two patients became unresponsive and one became apneic, requiring intubation. Dextrorphan is no longer in clinical trials because of the sudden hypotension it can produce.

Several features of this study raise ethical concern. First is the number of patients who experienced significant adverse events before the study was completed. Dose-escalation studies are generally designed to carefully titrate doses upward in a limited number of patients and to stop when dose-limiting events are encountered. For instance, when new cancer agents are in phase 1 testing, a common paradigm is to expose only 3 to 6 patients to each successive dose and to halt the testing if more than 2 subjects experience grade 3 toxicity.<sup>40</sup> (Such a careful, step-by-step approach was used in a pilot study of rtPA in acute stroke.<sup>41</sup>) In the dextrorphan study, 21 patients received the maximal loading dose (200 to 260 mg/h IV), and 7 of these experienced symptomatic hypotension. Even if one accepts all of the other unpleasant side effects such as vomiting and hallucinations, the

number of patients suffering potentially harmful hypotension seems excessive.

From both an ethical and a practical perspective, the most challenging aspect of this trial was the timing of drug administration. NMDA antagonists had been reported to be effective in animal models of focal ischemia only when given within 2 to 3 hours of stroke onset. One study performed in the early 1990s reported a trend toward *worse* outcomes with dextrorphan than with placebo when administered to rabbits as little as 4 hours after stroke onset.<sup>42</sup> Although the therapeutic window for neuroprotective agents remains uncertain in humans, most experts have put it far short of 31 hours, the mean interval to the initiation of treatment in this study.<sup>43,44</sup> If this estimate of the therapeutic window is even close to correct, there could be little if any expectation that these patients would benefit medically from receiving dextrorphan. From their perspective, toxicity was the only likely outcome.

There are two ethical issues raised specifically by the decision to administer the drug to patients in the acute phase of their strokes but after the putative therapeutic window had passed. The first concerns the effect that the delay in administration had on the risk-benefit ratio for the experimental subjects, and the second concerns the patients' ability to give an informed consent.

There has been a tremendous effort at public education and streamlined care delivery to facilitate enrollment of patients in *therapeutic* stroke trials as rapidly as possible, since even small delays in drug administration may deny patients their best chance for benefit and thus cause the study to miss a drug's advantage over placebo.<sup>7,45-47</sup> Those enrolled in the dextrorphan study may have been patients who arrived too late for phase 2 or 3 studies and were deemed suitable for a study in which the primary scientific goal (evaluation of pharmacokinetics and toxicity) was less time sensitive. Unfortunately, such a delay virtually eliminated the chance that the new drug would help these patients and left only the risk of side effects, if not injury. In this circumstance, the physician's duties to do no harm, to advocate for his patient's best interests, and to avoid risks without commensurate benefits were superseded by the quest for pharmacologic data.

An evaluation of the risk-benefit ratio was not only incumbent on the treating physicians but was one of the primary tasks, and the major ethical duty, of the IRBs where this research was conducted.<sup>48</sup> IRBs are expected to disapprove research when the risks to patients are judged to be unreasonable in relation to the anticipated benefits.<sup>48</sup> If the IRBs failed to grasp the critical effect that timing had on the risk-benefit ratio in acute stroke therapy, they may have been too willing to tolerate the foreseeable toxicity of dextrorphan for these patients.

The second ethical issue related to timing concerns the capacity of these patients to meaningfully consent to participate in such a study, and more particularly their ability to distinguish between interventions with real therapeutic potential for themselves and interventions in which the risks of toxicity were high and the potential for benefit remote. As I will describe, there are a number of barriers to consent in stroke patients, even those who are alert, and the ability to gain consent is especially problematic when one is conducting phase 1 trials.

## The Stroke Patient as Research Subject

The issue of whether an individual has the capacity to provide informed consent to treatment is familiar to all who see acutely ill patients. Such patients are under stress and vulnerable—suddenly ill, fearful, and likely to trust their caregivers implicitly to do what is best for them. In the case of stroke patients in particular, aphasia, decreased alertness, and preexisting deficits may all impair comprehension. One stroke researcher has written that, on a neurologic basis alone, most stroke victims are incapable of giving informed consent.<sup>49</sup> When the time pressure imposed by the short therapeutic windows of many new drugs is added, it is all the more difficult to secure ethically valid consent for treatment, let alone for participation in an experimental trial.

Recognizing the difficulties with informed consent in the acute stroke setting, particularly when patients are cognitively impaired, many treating physicians and investigators will turn to close relatives to secure a proxy (or surrogate) consent to treat the patient or to enroll him or her in a clinical trial.<sup>5</sup> Although the legal status of proxy consent for research is not well defined in many states,<sup>50</sup> California and New York appear to draw a distinction between therapeutic research, in which proxy consent may be valid, and "nontherapeutic" research (ie, research providing no prospect of direct benefit to individual subjects), in which proxy consent has unclear validity.<sup>51,52</sup> Whether permitted by law or not, the American College of Physicians explicitly disapproves surrogate consent for nontherapeutic experimentation that presents more than a minimal risk of harm or discomfort.<sup>53</sup>

New federal regulations allow a waiver of consent altogether for studies in emergency situations in which life is threatened and an investigational treatment offers the prospect of direct benefit to the subject.<sup>54</sup> These rules appear to remove a barrier to enrollment in phase 2 and phase 3 stroke trials<sup>55</sup>; however, once again, they would not reasonably apply to toxicity trials if there is no prospect of patient benefit.

In sum, both legal and ethical considerations should severely limit the enrollment of cognitively impaired stroke patients in toxicity trials, even if family members can be found who will consent to such studies.

Finally, there are problems that may arise when the treating physician and the researcher are the same person or part of the same team. In this situation the acutely ill patient or his family cannot always distinguish between standard treatments, therapeutic trials, and toxicity studies.<sup>56</sup> They will usually do what the doctor recommends. Of course, the duty of the treating physician is to promote and safeguard the patient's welfare. But given the dual role of physician and scientist, conflicts may arise between this duty and the goals of the investigation.<sup>57</sup> Because of this potential for conflict of interest, many commentators have advised that the roles of treating physician (or team) and researcher be separated,<sup>57,58</sup> especially in phase 1 studies, where patients routinely mistake what they undergo as receiving therapy.<sup>56,59,60</sup>

## Discussion

The balancing of ethical and logistic considerations makes the design and conduct of acute stroke trials more difficult than many other areas of clinical research. As shown in the

NINDS rtPA trial, the design of an efficient double-blind controlled study may conflict with strict ethical constraints regarding both potentially risky interventions to promote patient enrollment and the optimal treatment of patients assigned to the control group. The dextrorphan study highlights the more classic conflict between the desire to learn how these new drugs might be tolerated by stroke patients in general and the duty to protect the immediate patients/subjects from undue harm. In all stroke studies, securing the patients' consent is difficult because the time frame for intervention is so short and the patients are suddenly ill and may be cognitively impaired. If, as in many institutions, stroke specialists or teams both provide the care and conduct the research, a time-saving efficiency is accomplished, but only through giving physicians the conflicting roles of caregiver and researcher.

I believe the NINDS study ventured onto ethically debatable ground when the decision was made to reduce patients' BP (however carefully) so they could qualify for the trial. Further, the continued treatment of hypertension in control patients added an unconventional risk to their care that was not medically or ethically justified.

The dextrorphan study demonstrates what willing stroke patients may be asked to endure for the sake of scientific advancement—a toxic ordeal not redeemed by any likely medical benefit. It is a troubling picture that leads me to suggest the application of the following very strict guidelines for the conduct of phase 1 research involving acute stroke patients:

(1) Because of formidable problems in obtaining informed consent, dose-escalation/toxicity studies of new stroke drugs should be undertaken and completed in normal healthy volunteers or in patients sufficiently beyond the acute phase of illness to minimize misunderstanding of the nontherapeutic nature of the research.

(2) If dose-escalation studies must be done in acute stroke patients, several safeguards should be in place: (a) The IRB should consider these patients as a "vulnerable population" and impose additional safeguards that in its judgment are appropriate to the research.<sup>61</sup> (b) The IRB should be clearly informed of the critical importance of the timing of drug administration so it can properly evaluate the risk/benefit ratio for potential enrollees. (c) A protocol of carefully monitored dose escalation should be employed. (d) Only stroke patients with intact decision-making capacity should be recruited. Proxy consent for enrollment, especially beyond the likely therapeutic window, should not be permitted. (e) There should be a physician responsible for the patient's care who is not a part of the research team.

### Conclusion

The emergence of many factors—the high prevalence and devastation of stroke, recent advances in understanding the pathophysiology of ischemic injury, a cadre of dedicated researchers, major investments by the pharmaceutical industry—has led to a flowering of clinical research unprecedented in the area of stroke. While several trials of thrombolytic and neuroprotective agents have already been completed, many more are under way or expected in the next decade. The era of nihilism in stroke is, thankfully, over.

At the same time, we must remember that at least five large studies of thrombolytic and neuroprotective agents, involving thousands of patients, have been stopped when the complications of experimental treatment appeared unacceptable.<sup>21,62–65</sup> The experience of patients in one phase 1 trial has been described earlier. Therefore, participation in acute stroke research thus far has proved to be a risky undertaking for many patients.

Those engaged in stroke research are aggressively pursuing the twin goals of improved care and better outcomes for stroke victims, which cannot be reached without clinical trials involving thousands of patients. Those conducting such trials surely view them as opportunities to offer patients the latest and most hopeful interventions and are anxious to proceed as quickly as possible. However, this enthusiasm must be tempered by a candid assessment of the risks to which patients will be exposed and a sensitivity to the ethical complexity of studying such an acutely ill and vulnerable population.

As the philosopher Hans Jonas wrote nearly 30 years ago,

Let us not forget that progress is an optional goal, not an unconditional commitment, and that its tempo in particular, compulsive as it may become, has nothing sacred about it. Let us also remember that a slower progress in the conquest of disease would not threaten society, grievous as it is to those who have to deplore that their particular disease be not yet conquered, but that society would indeed be threatened by the erosion of those moral values whose loss, possibly caused by too ruthless a pursuit of scientific progress, would make its most dazzling triumphs not worth having.<sup>66</sup>

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