Urgent Therapy for Stroke

Part II. Pilot Study of Tissue Plasminogen Activator Administered 91–180 Minutes From Onset

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Background and Purpose: Renewed interest in thrombolytic therapy as potential treatment for patients with acute ischemic stroke prompted a dose-escalation safety study of tissue plasminogen activator in patients with very early (≤90 minutes; see Part I) neurological symptoms. To test whether this stringent entry window might be safely lengthened, a second study was organized to test tissue plasminogen activator in patients with symptoms of 91–180 minutes’ duration before treatment.

Methods: An open-label, dose-escalation design was chosen. Eligible patients had pretreatment head computed tomographic scanning and treatment began 91–180 minutes from stroke onset. End points examined included the incidence of symptomatic and asymptomatic intracranial hemorrhage, other bleeding, and clinical outcome at 2 hours, 24 hours, and 3 months after treatment.

Results: Twenty patients were treated at three hospitals in 13 months. Three doses were tested: 0.6 mg/kg (n=8), 0.85 mg/kg (n=6), and 0.95 mg/kg (n=6). Two patients, one each at the two highest doses, sustained fatal intracerebral hemorrhages. Three patients (15%) improved by ≥4 points on the National Institutes of Health Stroke Scale by 24 hours.

Conclusions: These observations suggest that tissue plasminogen activator treatment of acute ischemic stroke 91–180 minutes from onset in doses of 0.85 mg/kg is attended by a risk of intracerebral hemorrhage approximating 17% (range 3–44%, 95% confidence interval). The rate of early neurological improvement observed in this study was small but does not exclude an improvement over the natural history. Future study with placebo control subjects and stratification by time to treatment is indicated.

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KEY WORDS  • cerebral ischemia  • plasminogen activator, tissue type  • thrombolytic therapy

Thrombolytic therapy for acute cerebral infarction has received renewed interest in the last decade.1,2 With the development of newer therapeutic agents, such as recombinantly produced human tissue plasminogen activator (rt-PA, Genentech, Inc., South San Francisco, Calif.), the prospect of reperfusing a region of ischemic brain destined for imminent infarction has become an enticing idea for reducing the toll of death and neurological disability exacted by acute stroke. The safety of this approach has not been established, however, and older studies have reported an unacceptably high rate of fatal intracerebral hemorrhage complicating thrombolytic therapy.3,4

In February 1987 accrual began at three participating centers in the first of two pilot studies of intravenous rt-PA therapy for patients with acute ischemic neurological deficits. The objectives of this study were two-fold. The primary objective was to find the highest safe dose of rt-PA that might be administered to patients with evolving cerebral infarction. Therefore, an open-label, dose-escalation design was selected. A secondary objective was to accomplish very early treatment after the onset of symptoms in an attempt to maximize the safety and potential efficacy of the therapy. A maximum of 90 minutes after the onset of symptoms was thought to be the earliest feasible time for intervention, if the centers were properly prepared.

From February 22, 1987, through September 15, 1989, 74 patients were successfully accrued to the first study. Details of patient selection, study design, and the results are reported in Part I.5 However, these 74 patients represented only 9.2% of all patients suspected initially to have acute (<24 hours) ischemic infarctions admitted to the participating centers during that time. Although the precise interval beyond which ischemic brain tissue becomes irreversibly damaged has not been determined in humans, several reports have described clinical im-

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were identical to the protocol for Part I, including the two protocol modifications excluding patients with clinical pericarditis and those with mean blood pressures >133 mm Hg that were developed during the course of performing the first study. All final determinations regarding patient eligibility were made by a neurological investigator on call.

Pretreatment screening and posttreatment evaluations and management protocols were identical to those used for patients treated within 90 minutes. The patients were carefully monitored for bleeding complications, and neurological status was evaluated with serial National Institutes of Health (NIH) Stroke Scale scores, as well as functional outcome ratings at 7–10 days and 3 months. Ischemic stroke type was classified by the participating investigators according to the same clinical criteria used in patients treated within 90 minutes. Heparin use was prohibited until at least 30 minutes after the rt-PA infusion stopped and then only after a repeat computed tomographic (CT) scan demonstrated no hemorrhage. Bolus heparin was prohibited for the first 6 hours following treatment. All heparin use was carefully documented.

Results

From December 1988 through December 1989, 20 patients were accrued to the open-label, 91–180 minute limb of the study at three hospitals (New York Hospital, Winchester [Virginia] Medical Center, and University of Virginia Hospital). To recruit these 20 patients, 317 patients with suspected ischemic stroke within 24 hours from onset were screened at the participating hospitals. Ninety-one patients arrived at the study hospitals at 45–150 minutes from onset. All eligible patients and/or families gave informed consent before participating. Table 2 details the age, race, and sex of the patients; the families gave informed consent before participating. The ischemic stroke type was determined by the participating investigators according to the same clinical criteria used in patients treated within 90 minutes.

The mean age of the patients was 65 ± 17 (SD) years, 65% were men, and 80% were white. Fifty percent were believed to have had large vessel atherothrombotic infarctions, and another 40% were thought to have cardioembolic infarctions. The remaining 10% had lacunar infarctions. In contrast to the ≤90-minute group, no patients were judged to have had large vessel athroembolic infarctions, although angiograms were performed in only 25% of patients in this series. The mean time from onset of stroke symptoms to initiation of treatment was 138 ± 20 minutes, and these times were normally distributed. The mean time from stroke onset to arrival in the participating hospital emergency room for the 19 patients with out-of-hospital stroke was 73.7 ± 22.6 minutes (range 42–125 minutes). The mean time from emergency room arrival to initiation of treatment was 65.0 ± 13.7 minutes (range 55–110 minutes).

Table 3 summarizes the dose, baseline NIH Stroke Scale scores, and all bleeding complications noted. The mean baseline Stroke Scale score was 17 ± 7. Two patients, one at 32 mg/m² (0.85 mg/kg) and one treated with 37.6 mg/m² (0.95 mg/kg), sustained intracerebral hemorrhages, both fatal (Figure 1). The first hemorrhage was located in a region of brain not involved clinically by the presenting cerebral infarction, whereas

### Table 1: rt-PA Dose Tiers

<table>
<thead>
<tr>
<th>Dose tier*</th>
<th>rt-PA dose</th>
<th>Duration (min)</th>
<th>Dose cap (mg)</th>
<th>Bolus dose†</th>
</tr>
</thead>
<tbody>
<tr>
<td>II</td>
<td>22.6 mg/m² (0.6 mg/kg)</td>
<td>60</td>
<td>60</td>
<td>10%</td>
</tr>
<tr>
<td>IV</td>
<td>32 mg/m² (0.85 mg/kg)</td>
<td>60</td>
<td>90</td>
<td>10%</td>
</tr>
<tr>
<td>IV-E‡</td>
<td>37.6 mg/m² (0.95 mg/kg)</td>
<td>90</td>
<td>90</td>
<td>None</td>
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</tbody>
</table>

rt-PA, recombinant tissue plasminogen activator.
*Roman numerals conform to dose tiers reported in ≤90-minute group."†Ten percent of total dose given as rapid bolus at initiation of treatment; remainder infused over prescribed period.
‡Tier IV-E administered as 32 mg/m² (0.85 mg/kg) during first 60 minutes, then 5.6 mg/m² (0.10 mg/kg) over next 30 minutes.
Asymptomatic hemorrhagic conversion of the infarction was observed on the follow-up head CT scans in four of the 20 patients and occurred even at the lowest dose tier. The second patient's hemorrhage was located in a clinically involved brain. Minor extracranial bleeding (e.g., oozing from the gums) was observed in one third of patients and occurred even at the lowest dose tier. Asymptomatic hemorrhagic conversion of the infarction was observed on the follow-up head CT scans in four of the 20 patients and was not dose related.

The clinical outcomes of the patients by dose tier are summarized in Table 4. Five patients (25%) had major neurological improvement, defined as a ≥4-point improvement in the NIH Stroke Scale score, observed at 24 hours after beginning the infusion, but two of these relapsed within 24 hours. Three patients (15%) had a ≥4-point improvement in the NIH Stroke Scale noted at 24 hours (by 10, 12, and 13 points). Two of these patients were functioning at home with no limitation in activities of daily living at the 3-month follow-up. The third patient had neither improved nor deteriorated after rt-PA treatment. The fourth patient treated with heparin was anticoagulated 3 hours after rt-PA treatment at the tier IV dose. There had been complete recovery of neurological function at 2 hours. However, despite heparin treatment, symptoms relapsed, and the 24-hour Stroke Scale score was similar to the baseline score. Computed tomographic scans confirmed that none of the clinical deteriorations were due to intracranial hemorrhage. In summary, anticoagulation with heparin did not prevent relapse of neurological deficits after thrombolytic therapy in this series.

Six patients (30%) died during the 3-month follow-up. Two died of hemorrhagic complications associated with rt-PA therapy (see above), and three patients with large infarctions died of pneumonia or sepsis complicating their strokes. The sixth patient died of complications associated with a cerebral angiogram.

### Discussion

This article reports preliminary experience with the safety of several doses of rt-PA in 20 patients with acute ischemic stroke treated 91–180 minutes after the onset of focal ischemic neurological symptoms. As a supplement to a study in a larger cohort of 74 patients treated in a similar fashion but in ≤90 minutes from onset, the results provide some initial insights into the potential for extending the "therapeutic window" to make more patients eligible for treatment by this modality. Several observations and comparisons with the results from the ≤90-minutes group seem pertinent.

**Table 2. Patient Characteristics**

<table>
<thead>
<tr>
<th>Dose tier</th>
<th>Patient No.</th>
<th>Age (yr)</th>
<th>Race</th>
<th>Sex</th>
<th>Stroke type</th>
<th>Vascular territory</th>
<th>Symptom onset to treatment (min)</th>
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<tr>
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<td>1</td>
<td>80</td>
<td>W</td>
<td>F</td>
<td>CE</td>
<td>R MCA</td>
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<td>L MCA</td>
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<td></td>
<td>3</td>
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<td>6</td>
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<td>M</td>
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<td>AT</td>
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<td>La</td>
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<tr>
<td>IV-E</td>
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<td>B</td>
<td>M</td>
<td>CE</td>
<td>L MCA</td>
<td>175</td>
</tr>
</tbody>
</table>

W, white; B, black; O, Oriental; F, female; M, male; CE, cardioembolic; AT, large vessel atherothrombotic; La, lacune; R, right; L, left; MCA, middle cerebral artery; LS, lenticulostriate; VB, vertebrobasilar; PCA, posterior cerebral artery.

*Indicates patients who improved by ≥4 points on the National Institutes of Health Stroke Scale at 24 hours.
First, a dose-related risk of intracerebral hemorrhage was not noted statistically, but too few end points were observed to be conclusive. Although the confidence limits are broad because of the small numbers of patients, the risk of symptomatic intracranial hemorrhage in this series was 10% overall and 17% at the two higher dose tiers. If further experience confirms that these figures approximate the true risk of intracerebral hemorrhage, the therapeutic benefit of reperfusion therapy, already established for acute ischemic stroke, might be limited to patients with a low risk of hemorrhage.

(rt-PA, recombinant tissue plasminogen activator; ASX, asymptomatic.

*National Institutes of Health Stroke Scale scores.

FIGURE 1. Head computed tomographic scans obtained shortly after neurological worsening in (panel A) a 75-year-old, right-handed, hypertensive, diabetic woman treated 120 minutes after onset of acute aphasia and right hemiparesis. Hemorrhage into right thalamus and adjacent white matter with intraventricular extension resulted in coma and decerebrate posturing, from which she never recovered. Panel B: A 67-year-old right-handed woman began treatment 155 minutes after onset of aphasia and right hemiparesis. One hour after rt-PA infusion was completed, drowsiness and increased right hemiparesis signaled onset of hemorrhage into left striatum with intraventricular extension. The bleeding was associated with severe hypofibrinogenemia (51 mg/dl).
hemorrhage from this therapy, then considerable clinical benefit would need to be demonstrated to justify the treatment risk. Unfortunately, in this small series dramatic clinical improvement was observed at 24 hours in only 15% of patients, and whether the observed clinical improvement was, in fact, due to successful recanalization of an occluded cerebral artery remains conjectural. Compared with the 46% improvement rate at 24 hours observed with treatment in the ≤90-minutes group, the difference in proportion of patients with early neurological improvement was statistically significant (p<0.01, Fisher’s exact test). The groups may not have been entirely comparable, since the baseline Stroke Scale score was significantly worse (17±7 vs. 13±7, p<0.05, t test) in the 91-180-minute group. Nevertheless, the observed rate of improvement may still be better than the natural history of the disease, about which there is little information in these very early time periods.

As with the ≤90-minutes group, asymptomatic hemorrhagic conversion of infarction detected by head CT scanning was not an rt-PA dose-related phenomenon. No patient with asymptomatic hemorrhagic change had early clinical improvement. Others have reported spontaneous hemorrhagic conversion of large cerebral infarctions in the absence of reperfusion with thrombolytics or use of anticoagulants. 31

One methodological concern that was raised during the design of this study was that there may be a tendency for treating investigators to ignore the urgency with which the patients in this cohort need to be treated, resulting in possible clustering of patients treated at the 180-minute time limit. The results, however, argue that the investigators were able to successfully adhere to the discipline of time, since the intervals from onset to treatment were normally distributed about a mean of 138 minutes. Because delays in treatment may have an adverse impact on outcome, these results are encouraging from the standpoint of the design of future trials and the development of future clinical practice.

The trial was terminated after the sixth patient was accrued in the third tier. Further testing at higher doses was not undertaken because of concerns raised in the ≤90-minutes group experience about the safety of higher doses. The experience in the >90-minutes group demonstrated that treatment at a dose of 0.85 mg/kg, a dose that was safe in 20 patients treated within 90 minutes, was associated with a risk of intracerebral hemorrhage in one of the six patients treated. Nevertheless, this dose approximates the dose administered in the first hour in patients with acute myocardial infarction and has documented efficacy in lysing coronary artery thrombi.12-13 We propose that this dose undergo further testing of safety and efficacy in future randomized, placebo-controlled trials. Stratification of patients by time from onset to treatment is recommended in view of the potential differences in safety and efficacy suggested by these results.

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The authors wish to express their gratitude and appreciation to the rescue squads and emergency medical personnel at each of the participating hospitals, without whose dedicated efforts this work would not have been possible. The authors also thank Drs. Thomas Price, John Hallenbeck, and David Stump for their helpful advice.

References

7. Mori E, Tabuchi M, Yoshida T, Yamadori A: Intracarotid uroki

TABLE 4. Clinical Outcome

<table>
<thead>
<tr>
<th>Dose tier</th>
<th>Patients</th>
<th>No. with MNI at 2 hours</th>
<th>No. with MNI at 24 hours</th>
<th>Outcome at 3 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>II</td>
<td>20</td>
<td>8</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>IV</td>
<td>6</td>
<td>1</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>IV-E</td>
<td>6</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

MNI, major neurological improvement (improvement of ≥4 points in National Institutes of Health Stroke Scale score); D, Dead; NL, no limitation in activities of daily living; Mild L, mild limitation; Mod L, moderate limitation; LTF, lost to follow-up.

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