Intravenous Tissue Plasminogen Activator for Acute Ischemic Stroke
A Canadian Hospital’s Experience

Kristine M. Chapman, MD; Andrew R. Woolfenden, MD; Douglas Graeb, MD; Dean C.C. Johnston, MD; Jeff Beckman, MD; Michael Schulzer, PhD; Phil A. Teal, MD

Background and Purpose—In the United States, tissue plasminogen activator (tPA) was approved for treatment of acute ischemic stroke in 1996. Its use has only recently been approved in Canada. We sought to evaluate the safety, feasibility, and efficacy of treatment in a Canadian hospital setting.

Methods—A combined retrospective and prospective review is presented of 46 consecutive patients treated with intravenous tPA at our hospital with a treatment protocol similar to that of the National Institute of Neurological Disorders and Stroke (NINDS) trial.

Results—Symptomatic intracranial hemorrhage at 36 hours occurred in 1 patient (2.2%). The median time to treat was 165 minutes, with a median “door-to-needle” time of 84 minutes. Compared with patients presenting initially at our hospital, patients transferred from another institution for tPA therapy were treated closer to the 3-hour time window (mean 173 versus 148 minutes, \( P < 0.001 \)) but had a shorter door-to-needle time (43 versus 102 minutes, \( P < 0.001 \)). For every 10 minutes closer to the 3-hour time window that any patient arrived at the hospital, 7 minutes was saved in the door-to-needle time (correlation coefficient 0.9, \( P < 0.001 \)). Patient outcome did not differ from that in the NINDS trial (\( P > 0.75 \)).

Conclusions—Our safety and patient outcome data compare favorably with NINDS and Phase IV data. Although a 3-hour treatment window was feasible, the median door-to-needle time lengthened as more treatment time was available and the door-to-needle time was beyond recommended standards. This review has prompted changes in our community to improve treatment efficiency. (Stroke. 2000;31:2920-2924.)

Key Words: Canada ■ stroke, ischemic ■ thrombolytic therapy

The administration of intravenous tissue plasminogen activator (tPA) within 3 hours of acute ischemic stroke onset received approval from the Food and Drug Administration in the United States in 1996 that was based on the positive National Institute of Neurological Disorders and Stroke (NINDS) tPA trial.\(^1\) The clinical benefit of tPA is sustained at 1 year.\(^2\) Some controversy remains because other thrombolytic trials have failed to establish efficacy, albeit with longer time windows and different protocols.\(^3\)\(^-\)^\(^5\) However, recent meta-analysis data for patients treated within 3 hours of stroke in the European Cooperative Acute Stroke Study (ECASS) I, ECASS II, and NINDS trials and reanalysis of ECASS I data using NINDS outcome measures provide further evidence of clinical benefit.\(^6\)\(^,\)^\(^7\) In addition, there is growing postmarketing experience in the United States demonstrating the safety and effectiveness of intravenous tPA in routine clinical practice.\(^8\)\(^-\)^\(^12\)

Health Canada has granted provisional approval for the use of tPA in acute ischemic stroke (February 1999) providing that postmarketing surveillance is in place. Currently, there is very limited experience to address the questions of safety and efficacy of tPA use in our country.\(^11\)\(^,\)\(^13\) Significant differences in patient access to acute stroke therapy exist in Canada compared with the United States.\(^13\)\(^,\)\(^14\) Technology and stroke expertise are centralized, restricting thrombolytic use and necessitating protocols for rapid patient transfer to capable sites.

In 1996, we instituted a tPA protocol, established a hospital stroke team, and developed rapid transfer policies at local referring hospitals. The purpose of the present study was to assess our center’s experience with intravenous tPA for acute ischemic stroke by reviewing safety data, the feasibility of a 3-hour time window, and patient outcome in this setting.

Subjects and Methods
The Vancouver Hospital and Health Sciences Center (VHHSC) is a tertiary care referral center and the main teaching hospital for the University of British Columbia. A system for rapid patient triage and...

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stroke team notification is in place. The number of the stroke pager is posted in all local feeder hospital emergency rooms (ERs). Patients presenting to our ER and several local community hospitals are screened for eligibility by telephone. The stroke team consists of 3 neurology faculty members, 3 nurse coordinators, and neurology residents. An attending neurologist on the stroke team assesses all potentially eligible patients.

We conducted a retrospective chart review of all patients (n=29) receiving intravenous tPA for acute stroke at VHHSC from May 1996 to February 1999 and a prospective review of all patients treated subsequent to the Canadian approval of tPA for acute ischemic stroke to January 1, 2000 (n=17). A tPA protocol based on established guidelines was used and approved by the hospital ethics committee. Patients were generally excluded if the initial CT scan demonstrated hemorrhage, significant mass effect, or early signs of infarction suggesting involvement of >1/3 of the middle cerebral artery (MCA) territory. Informed consent was obtained from the patient and/or family member in all cases. Patients underwent a CT scan 24 hours after treatment. Additional CT scans were obtained if the patient deteriorated clinically. At the time of treatment, the initial CT scans were evaluated by the stroke neurologist and, when available, a neuroradiologist. Additionally, all available CT scans (n=41) were evaluated retrospectively by one neuroradiologist to determine signs of early infarction and CT scan protocol violations.

Records were reviewed to obtain demographic information, stroke risk factors, admission and maximum blood pressure, time to arrival in the ER, laboratory parameters, and medications. Stroke subtype was determined according to Treatment of Acute Stroke Trial (TOAST) criteria. Initial stroke severity was determined by use of the NIH stroke scale (NIHSS). The modified Rankin Scale (mRS) and Barthel Index (BI) scores were recorded at discharge and obtained by subsequent telephone interview in all surviving patients.

Time analyses were performed on the entire group and were also stratified for mode of hospital arrival (direct to VHHSC versus transfer from a local hospital). A Kaplan-Meier survival analysis was used to compare the stroke onset to treatment times for patients presenting directly to VHHSC and for patients referred from other hospitals. A log-rank test was performed to determine whether there was a significant difference between the treatment times of these subgroups. Similarly, the differences between the time of stroke onset to ER presentation in each subgroup were compared. The 4 patients who suffered strokes while they were inpatients at VHHSC were excluded from the arrival time analysis. A Fisher exact test was used to compare our hemorrhage rate with that of the NINDS treatment arm. Patient outcome and mortality data were compared with data from the NINDS treatment cohort by use of a χ2 test. The efficiency of the stroke team was assessed by regression analysis, which related the time required to treat a patient (“door-to-needle” time) with the time lapse from stroke onset to ER arrival. ANCOVA was used to compare differences between patients presenting at VHHSC and those referred from elsewhere. ANCOVA was also applied to the door-to-needle times of these 2 subgroups regressed on chronological time to determine whether treatment times improved as more experience was gained.

## Results

### Patient Population

Twenty-nine patients presented initially at VHHSC (63%), and 17 were transferred from community hospitals (37%). This represents 1.8% of all ischemic strokes seen at our institution over this time period. The demographics and stroke risk factors of our patients were similar to those in the treatment group of the NINDS trial (Table). The mean age was 67±11 (range 42 to 84) years. The median pretreatment NIHSS was 14 (range 3 to 35). Fourteen (30%) patients were on aspirin at the time of stroke, and 1 (2%) patient was on ticlopidine.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Vancouver</th>
<th>NINDS Treatment Arm (Part B)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, y</td>
<td>67±11</td>
<td>69±12</td>
</tr>
<tr>
<td>Female, %</td>
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<td>43</td>
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<tr>
<td>Ethnic group, %</td>
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<tr>
<td>Hispanic</td>
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</tr>
<tr>
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<td>1</td>
</tr>
<tr>
<td>NIHSS (median)</td>
<td>14</td>
<td>14</td>
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<tr>
<td>Stroke subtype, %</td>
<td></td>
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</tr>
<tr>
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<td>14</td>
</tr>
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<td>39</td>
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<tr>
<td>Blood pressure, mm Hg</td>
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<tr>
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<td>153</td>
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<tr>
<td>Diastolic</td>
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<td>85</td>
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<tr>
<td>Stroke risk factors, %</td>
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<td>67</td>
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<tr>
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<td>12</td>
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<tr>
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<td>20</td>
</tr>
<tr>
<td>Prior MI</td>
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<td>22</td>
</tr>
<tr>
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<td>20</td>
</tr>
<tr>
<td>Prior CHF</td>
<td>17</td>
<td>16</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
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</tr>
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</table>

MI indicates myocardial infarction; CHF, congestive heart failure.

### Safety

Symptomatic intracranial hemorrhage during the first 36 hours occurred in 1 (2.2%) patient. The symptomatic intracranial hemorrhage rate did not differ significantly from that in the NINDS trial (P=0.50). The patient with symptomatic intracranial hemorrhage was 84 years old and had a pretreatment NIHSS of 24. His maximum blood pressure reading was 170/80 mm Hg, and glucose was 6.7 mmol/L. The initial CT scan showed signs of early infarction (<1/3 of the MCA territory) but no mass effect. The 24-hour CT scan demonstrated a large infarction involving virtually the entire left MCA territory. There was a parenchymal hemorrhage with ventricular extension, mass effect, and obstructive hydrocephalus. The patient died 3 days after treatment. Three other patients (7%) suffered non–life-threatening systemic hemorrhage within 10 days of treatment, 1 of whom required a transfusion.

Signs of early infarction were noted on 24 of 41 scans available for review, and a dense MCA sign was present in 16 cases. On the 24-hour scan, an acute infarction was apparent in 35 patients. Three patients had initial early infarction in >1/3 of the MCA territory.

Nine protocol violations occurred in 8 patients. There were 5 protocol violations for time >180 minutes (181, 182, 185,
Feasibility

The median time from stroke onset to treatment for all patients was 165 (range 70 to 190) minutes. The mean time from stroke onset to treatment for patients presenting directly to our ER was 148 (median 148) minutes versus 173 (median 176) minutes for patients transferred from elsewhere (P<0.001). The median time from arrival to CT scan for all patients was 67 minutes. The median door-to-needle time for all patients was 84 (range 19 to 140) minutes. Patients presenting directly to our ER took an average of 46 minutes to arrive and had an average door-to-needle time of 102 minutes. In contrast, it took patients transferred from elsewhere longer to arrive at our ER (average of 130 minutes), but the average door-to-needle time was faster at 43 minutes (P<0.001). Fourteen patients had a door-to-needle time of <60 minutes, all of whom were transferred from other institutions.

There was an inverse relationship between the time from stroke onset to ER arrival and the door-to-needle time (Figure 1). Overall, for each 10-minute delay in arrival, there was a decrease in the door-to-needle time of 6.7 minutes (correlation coefficient 0.9, P<0.001). For patients coming directly to our ER, each 10-minute delay in arrival resulted in a decrease in the door-to-needle time of 5 minutes (P=0.03). For patients transferred from other hospitals, each 10-minute delay in arrival resulted in a decrease in the door-to-needle time of 6 minutes (P<0.001).

Four patients in our series were inpatients at VHHSC at the time of stroke onset; 2 strokes occurred in the ER after the patients presented with a transient ischemic attack, and 2 began on a hospital ward. The onset-treatment times in the ER patients were 80 and 65 minutes; the onset-treatment times for the ward patients were 174 and 180 minutes. Both patients whose strokes occurred in the ER were observed for a period of time before treatment to exclude recurrent transient ischemic attack. Delayed treatment of the ward patients was the result of slow stroke service contact time followed by difficulty in initiating thrombolytic therapy in a non-ER setting.

There was no significant improvement in the door-to-needle time over the course of the present study. The most common reasons that tPA was not administered included time >3 hours and spontaneous rapid improvement of stroke symptoms.

Outcome

At the time of hospital discharge, 30% of the patients had a favorable outcome on the mRS (score 0 to 1), and 37% had a favorable outcome on the BI (score 95 to 100). At the time of follow-up (median 13 months after stroke), 43% of the patients had a favorable outcome on the mRS, and 48% had a favorable outcome on the BI (score 95 to 100) (Figure 2). The differences between the mRS and BI scores in the VHHSC patients at follow-up compared with the NINDS treatment group at 1 year were not statistically significant (mRS, P=0.75; BI, P=0.78).

Ten patients (22%) died before discharge, which was comparable to 17% at 3 months in the NINDS trial (P=0.46). One hospital death was due to intracranial hemorrhage; 5, to cerebral edema with mass effect; 2, to respiratory failure (1 aspiration pneumonia); 1, to recurrent stroke; and 1, to multiorgan failure (congestive heart failure and renal failure). Two of the patients who died before discharge had protocol time violations (181 and 185 minutes). At 13 months, 22% of our patients were dead. This did not differ from the NINDS 1-year treatment cohort (24%, P=0.73).

Discussion

Intravenous tPA for acute ischemic stroke has only recently been approved for use in Canada. The lengthy approval process was mainly due to safety concerns expressed by Health Canada, the nation’s therapeutics regulatory body. A postmarketing database has been established to record outcomes in Canadian patients, and data collection is ongoing.19 Our results add to the growing Phase IV data suggesting that tPA is safe in routine clinical practice and that the hemorrhage rate can equal or improve on the rate reported in the pivotal NINDS study. In the largest prospective series to date (Standard Treatment With Alteplase to Reverse Stroke [STARS], n=389), symptomatic intracranial hemorrhage at 36 hours occurred in 3.3% (95% CI 1.8 to 5.6) of patients,
similar to the 2.2% rate seen in our series. However, others have published higher hemorrhage rates, and in particular, protocol violations may predispose patients to higher bleeding rates. Although we observed 9 protocol violations in 8 patients, 5 were for treatment just past the 3-hour time mark (maximum time to treatment 190 minutes). In STARS, protocol violations occurred in 32.6% of patients, 13.4% of whom were treated at >3 hours. Although we do not recommend treatment past 180 minutes, on a pathophysiology basis, there is little difference between treating a patient at 180 versus 181 minutes, and in selected cases, we were prepared to marginally extend the treatment window. In the present study, the number of protocol violations decreased over time.

Our symptomatic intracranial hemorrhage rate was lower than that seen in the NINDS trial; however, the difference was not statistically significant. Although we had only a small number of patients in our series, this trend may be due to our treatment protocol, which was based on recommendations from several sources; thus, other “safety features” were added, most notably the CT exclusion criteria. We recognize that exclusion of patients with early infarction signs in >1/3 of the MCA territory is controversial among stroke specialists because these patients were included in the successful NINDS trial. However, ECASS I clearly demonstrated that the risk of hemorrhage increases if signs of early infarction are seen in >1/3 of the MCA territory before treatment (OR 3.5). Also, within ECASS I, most protocol violations involved treatment of patients who had CT exclusions, underscoring the difficulty in early CT interpretation. In our series, 2 patients were unknowingly treated in this situation. ECASS II demonstrated improved CT interpretation with pretrial radiology courses, suggesting that practice improves skills. Limiting the number of treating neurologists combined with attempts to review the films with a neuroradiologist when available may have minimized the number of CT treatment violations in our series.

The NINDS group has recently addressed the need for rapid administration of tPA. They demonstrate that tPA efficacy is time dependent. The OR for excellent outcome approaches 1.0 when treatment occurs near the 3-hour mark. In view of evidence suggesting that faster treatment yields better outcome, our median time to treatment of 165 minutes leaves room for improvement. Guidelines recommend a door-to-needle time of 1 hour. This target was achieved in 14 of 46 patients in our series, all of whom were transferred from other facilities. In this situation, the stroke neurologist and radiology department had advanced warning of the arrival of a transferred patient, resulting in a faster door-to-needle time. Although the door-to-needle time was significantly faster for these transferred patients, the median time from stroke onset to treatment was 28 minutes longer than in patients presenting directly to VHHSC.

Review of our series has demonstrated difficulties with timely thrombolysis, particularly in the cohort of patients transferred from other hospitals. Lack of CT scan availability and stroke expertise in our health care region necessitates patient transfer. It is unlikely that improving efficiency at our hospital will significantly shorten treatment times in the transferred patient group. Therefore, we have initiated strategies to shorten the time to arrival at our ER, including upgraded priority for ambulance response and stroke transfer combined with educational programs for local emergency physicians and nurses. Future projects include the creation of a destination hospital policy in addition to education of ambulance attendants and the public regarding stroke recognition. The major delay in treating patients presenting directly to our hospital occurred before CT scan. Most patients in this series were referred after ER physician assessment. Within our hospital, we have implemented rapid nursing and ER physician triage protocols to improve the time to stroke team notification. Although the number of in-hospital strokes was small (2 ward strokes), these patients had major delays in treatment (mean onset-treatment time 177 minutes) that were due to slow stroke team notification and problematic tPA use in a non-ER setting. Wards and physicians have been supplied with educational information describing the stroke team. Analysis of this series has therefore enabled us to implement changes to streamline therapy.

In general, a number of factors contribute to the delay in door-to-needle time, including ER triage, availability of a CT scanner and laboratory results, consultation with other physicians, and treatment of hypertension. Furthermore, our series confirms the finding in STARS that as the length of time available to treat increases, the door-to-needle time increases as well. In our series, almost 7 minutes less time was required to treat for each 10 minutes closer to the end of the 3-hour time window the patient arrived. Thus, we were capable of rapid treatment when necessary, but we procrastinated when more time was available.

Stroke physicians need to be aware of the “human” variable of procrastination. Human nature is such that there is increasing motivation to complete a task as a deadline approaches. Therefore, better emphasis of several deadlines may improve treatment time. To overcome the procrastination factor, we are instituting a time sheet for each patient (target times, derived from the Advanced Cardiac Life Support guidelines, are bracketed). Times recorded include the following: onset, ER arrival, door to triage (5 minutes), door to stroke team notification (10 minutes), door to ER physician assessment (10 minutes), door to CT (25 minutes), and door to treatment (60 minutes). Stroke team review of each case is expected to improve performance. The NINDS investigators feel that periodic review is beneficial.

Our outcome data are similar to the NINDS trial follow-up data at 1 year. There is no difference in our mortality rate at follow-up (median 13 months, mortality 22%) compared with the NINDS treatment group at 1 year (mortality 24%, P = 0.73). Because our series is not blinded and because there is no control group, we cannot provide evidence for the efficacy of treatment. In addition, the retrospective nature of the present study has inherent limitations.

In summary, in a Canadian teaching hospital setting, our safety and patient outcome data compare favorably with NINDS and Phase IV data. The median door-to-needle times lengthened as more treatment time was available and the door-to-needle time was beyond recommended standards.
The present review has enabled us to confirm safety and improve efficiency.

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References
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