Building a “brain attack” team to administer thrombolytic therapy for acute ischemic stroke

Michael D. Hill,* Phillip A. Barber,* Andrew M. Demchuk,* Robert J. Sevick,† Nancy J. Newcommon,* Teri Green,* Alastair M. Buchan*

Abstract

Before tissue plasminogen activator (tPA) was licensed for use in Canada, in February 1999, the Calgary Regional Stroke Program spearheaded the development and organization of local resources to use thrombolytic therapy in patients who had experienced acute ischemic stroke. In 1996 special permission was obtained from the Calgary Regional Health Authority to use intravenously administered tPA for acute ischemic stroke, and ethical and scientific review boards approved the protocols. After 3 years our efforts have resulted in improved patient outcomes, shorter times from symptom onset to treatment and acceptable adverse event rates. Areas for continued improvement include the door-to-needle time and broader education of the public about the symptoms of acute ischemic stroke.

Tissue plasminogen activator (tPA) was approved for the treatment of acute ischemic stroke in the United States in 1996 and in Canada in February 1999. Before Canadian approval, several Canadian centres, including Calgary, had gained early experience by participating in clinical trials of tPA for acute ischemic stroke. By special arrangement with the local health authority, Calgary began a program of open-label thrombolytic therapy for stroke in 1996.

The barriers to using tPA for acute ischemic stroke are dominated by the short time window: the drug must be administered within 3 hours of stroke onset. Patients must fulfill strict inclusion criteria because of the risk of symptomatic intracerebral hemorrhage. Another major impediment is the lack of public understanding of what the symptoms of stroke are. In the United States only 47% of randomly surveyed adults could identify a cardinal stroke symptom.1 If patients do not recognize their symptoms and get to hospital rapidly, they cannot be treated with thrombolytic therapy.

The organizational approaches to solving the time problem and other barriers required a team approach. Because tPA for acute stroke was licensed only recently, only a few centres have had the opportunity to develop programs for acute stroke. We describe the development of the acute stroke service in Calgary and our initial experience with intravenously administered tPA.

Program development

The Calgary Regional Health Authority began restructuring health care services in the early 1990s. In January 1996 all neurosurgical and neurological staff and services were centralized to the Foothills Medical Centre. This allowed us to organize acute stroke care at one hospital around a multidisciplinary team that included the stroke team, the department of neurology, the department of diagnostic imaging, the department of emergency medicine, the stroke unit and emergency medical services (EMS). A protocol modelled after that used in the National Institute of Neurological Disorders and Stroke rt-PA Study was developed applicable to the Calgary region. A pilot study, followed by ongoing treatment if safety concerns were met, was approved by the Medical Advisory Committee of the Calgary Regional Health Authority. After the first 20 patients an internal audit was conducted to assess the safety and complication rate of intravenous tPA therapy for acute ischemic stroke.
We identified 5 Rs constituting the essential elements of acute stroke care: recognition (the time taken by patients to recognize their symptoms and call for help), reaction (the time taken for EMS to respond), response (the time from emergency department admission and assessment to CT scanning), reveal (the time for the stroke team to respond) and reperfusion (the time taken to start thrombolytic therapy) (Fig. 1). Target interval times are given in Table 1. This approach is similar to the “Code Stroke” pathways developed elsewhere. Special provisions were arranged with the Calgary Regional Health Authority for funding of a “blocked bed” on the stroke unit. This bed, virtually filled by a “ghost” patient, can be physically filled at any time with a real patient who has had a stroke.

If the patient is a candidate for thrombolysis, he or she is moved immediately from the emergency department to the stroke unit, and another blocked bed is created instantly. The unit is called in advance to prepare the tPA infusion based on the patient’s weight. The development of the blocked bed allowed for rapid removal of patients with acute stroke from the emergency department. Although patients were treated in a stroke unit in Calgary, the emergency department or intensive care unit would be logical alternatives in other institutions.

In cooperation with the Heart and Stroke Foundation of Alberta/North West Territories, a campaign was launched to educate the public about the symptoms of stroke. Specifically, people who might experience any of the cardinal symptoms of stroke — sudden onset of one-sided weakness (face, arm or leg), sudden onset of sensory loss (face, arm or leg), sudden difficulty speaking or understanding speech, or sudden loss of vision — were instructed to call 911 and inform the dispatcher that they were having a stroke. Local radio stations, television stations and newspapers participated in the education campaign.

EMS were asked to change their dispatch procedures for a possible stroke. En route, the driver was asked to alert the emergency department. Paramedics were taught a quick stroke assessment examination to identify patients who might be candidates for thrombolytic therapy. The dispatch priority for acute stroke was changed to a level 1 emergency (lights and sirens). All patients with onset of symptoms of acute stroke within the previous 3 hours were to be brought to Foothills Medical Centre, bypassing other hospitals.

The emergency department staff were asked to triage stroke as a life-threatening emergency, with a nurse and emergency physician making a preliminary assessment and arranging for plain cranial CT scanning. By arrangement with the diagnostic imaging department, the patient with acute stroke was given priority for CT scanning. On the patient’s arrival in the emergency department, the stroke team, stroke unit and neurology service were all contacted automatically.

The stroke team, composed initially of the neurology resident on call and the neurologist on call, with support from one of us (A.M.B.), now also has a stroke nurse-practitioner and 1 of 4 neurologists (2 staff, 2 fellows). The team meets the patient in the emergency department or at the CT scanner and assesses the patient for possible thrombolysis.

Over 100 neuroscience nurses on the acute neuro-observation unit were trained and certified in tPA administration in addition to basic stroke care in April and May 1996. The inclusion and exclusion criteria and the procedures for intravenous administration of tPA to patients with acute stroke were printed on a pocket-size card and distributed to all members of the department of neurosciences and the emergency department (Fig. 2).

In the expectation of an increase in the number of patients with transient ischemic attack (TIA) who would be seen in the emergency department as a result of rapid triage by EMS, a walk-in TIA clinic was scheduled every
weekday afternoon. All patients with TIs had a CT scan and were seen the same day or the following day in the stroke prevention clinic after direct referral from the emergency department. All information regarding treated patients was collected prospectively. We used the results of the original Oxfordshire Community Stroke Project cohort to estimate expected outcome.

Results

The first patient was treated with intravenously administered open-label tPA on Apr. 2, 1996. No safety concerns were identified at the internal audit after 20 patients had been treated. From the inception of the stroke program through Jan. 31, 1999, 69 patients were treated with intravenously administered tPA. The mean age was 69.3 years, 55% were male, 59% had a past history of hypertension, and 41% had atrial fibrillation. The median score on the National Institutes of Health Stroke Scale was 15. A total of 39% of the patients with total anterior circulation syndrome made an independent recovery at 3 months, as compared with 4% of the Oxfordshire patients. Similarly, 69% of the Calgary patients with partial anterior circulation syndrome, 50% of those with posterior circulation syndrome and 100% of those with lacunar syndrome achieved an independent outcome, as compared with 55%, 68% and 66% respectively of the Oxfordshire patients. The mean length of hospital stay was only 10.2 days, and 46% of the patients with stroke in Calgary patients with partial anterior circulation syndrome through Jan. 31, 1999, 69 patients were treated with thrombolytic therapy. The stated strict inclusion criteria resulted in a rate of symptomatic hemorrhage of 25%. Despite initial concerns and published guidelines, none of the patients with symptomatic hemorrhage required craniotomy. However, 83% of the patients with symptomatic hemorrhage were dead at the 90-day follow-up.

EMS was the only group to have treatment times equal to or less than our target times (Table 1). Once the patient arrived at the hospital, it took a mean time of 46.1 (range

| Table 1: Time intervals from symptom onset to treatment for 69 patients with acute ischemic stroke who received thrombolytic therapy in Calgary from April 1996 to January 1999 |
|---|---|---|---|---|
| Interval | No. of patients | Target | Mean | Median | Range |
| Symptom onset to emergency department | 63| 75 | 55.8 | 47 | 15–125 |
| Symptom onset to CT scanning | 68| 125 | 101.2 | 100 | 40–160 |
| Emergency department to CT scanning | 63| 30 | 46.1 | 37 | 5–130 |
| Emergency department to treatment | 63| 60 | 101.8 | 100 | 45–330 |
| CT scanning to treatment | 68| 30 | 55.6 | 45 | 20–315 |
| Symptom onset to treatment | 69| 135 | 157.1 | 160 | 100–405 |

*Times are approximately normally distributed.
†Six patients had a stroke while they were inpatients.
‡One patient was treated without a CT scan for presumed myocardial infarction.

<p>| Table 2: Types of stroke at Calgary Regional Health Authority (CRHA) adult acute care hospitals from April 1997 to March 1998* |</p>
<table>
<thead>
<tr>
<th>Stroke type†</th>
<th>CRHA total</th>
<th>Foothills Medical Centre</th>
<th>Peter Lougheed Centre and Rockyview Hospital</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemic stroke‡</td>
<td>731</td>
<td>468</td>
<td>263</td>
</tr>
<tr>
<td>Transient ischemic attack§</td>
<td>158</td>
<td>81</td>
<td>77</td>
</tr>
<tr>
<td>Subarachnoid hemorrhage¶</td>
<td>72</td>
<td>71</td>
<td>1</td>
</tr>
<tr>
<td>Intracerebral hemorrhage**</td>
<td>157</td>
<td>129</td>
<td>28</td>
</tr>
<tr>
<td>Total</td>
<td>1118†</td>
<td>749</td>
<td>369</td>
</tr>
</tbody>
</table>

*Source: corporate data, CRHA health records.
†International Classification of Diseases, Ninth Revision, Clinical Modification codes for most responsible diagnosis: 1433, 434, 436, 435, 430, 431. 432.
‡Nine patients were admitted directly to long-term care or the Alberta Children’s Hospital and are not included in this total.

| Table 3: Improvement in time intervals over time |
|---|---|---|---|
| Interval | Mean time, min | Mean of difference (and 95% confidence interval), min* |
| Symptom onset to emergency department | Apr 1996–Aug 1997 | Sept 1997–Jan 1999 | 15.0 (3.2 to 26.9) |
| Symptom onset to CT scanning | 113.3 | 89.7 | 23.6 (9.8 to 37.3) |
| Emergency department to CT scanning | 51.1 | 41.6 | 9.6 (–4.4 to 23.5) |
| Emergency department to treatment | 105.2 | 98.7 | 6.5 (–14.3 to 27.2) |
| CT scanning to treatment | 54.4 | 56.7 | –2.3 (–22.0 to 17.4) |
| Symptom onset to treatment | 167.8 | 147.4 | 20.3 (2.3 to 38.4) |

*Generated by means of a 2-sample t-test.
5–130) minutes to obtain a CT scan and a further mean
time of 55.6 (range 20–315) minutes to start tPA treatment.
The total mean time from symptom onset to treatment was
just over 2.5 hours (minimum 100 minutes). The times im-
proved over the study period (Table 3). Only 1 patient
(1%) was treated between midnight and 7 am; 27 (39%)
were treated on a weekend or holiday.

Interpretation

The main barrier to developing an acute ischemic stroke
service — availability of beds and nursing — was overcome
by the development of the blocked bed and an accompa-
nying salary for a neuroscience nurse. EMS were the first to
have their protocols operational, and although our records
are incomplete they indicate that, over the 3 years, only a
handful of patients were mistakenly sent to a hospital other
than the Foothills Medical Centre.

The neurology staff identified early on that they wanted to
take responsibility for clinical decisions while on call, with the
stroke team functioning in a consultative role. This arrange-
ment has worked particularly well, with each attending neu-
rologist participating actively in thrombolytic therapy.

Over 1 year, only 6% of patients with ischemic stroke ad-
mitted to Foothills Medical Centre and 4% of patients with
ischemic stroke in the region were treated with tPA. These
results compare favourably with those reported for Houston9
but leave much to be desired. Prospective information col-

---

**tPA in Acute Ischemic Stroke**

**Please contact STROKE TEAM**

**Procedures Prior to tPA Infusion**
- History and physical exam consistent with an acute ischemic stroke
- Pre-treatment tests: CBC, electrolytes, glucose, PT, PTT, fibrinogen, type and cross-match, ECG (results not required prior to tPA infusion unless suspected abnormality)
- Pre-treatment non-contrast head CT scan
- Attendance of the stroke physician to manage the case
- Compatibility with the inclusion criteria and contraindications (opposite page)

**Procedures: tPA Infusion and Subsequent Management**
- Infuse tPA in a 0.9 mg/kg (maximum 90 mg) continuous IV infusion over 60 minutes with 10% of total dose as a bolus at the start of infusion
- Monitor in an acute care setting for signs of neurological change or bleeding
  - BP q15min x 2h then q30min x 6h then q1h x 16h
  - Neurological signs q1h x 12h then q2h x 12h
  - Neurological examination (NIHSS or CNS score) q1h x 6h then q3h x 72h
  - Daily neurological evaluations after first 24h
  - NPO x 3h post infusion, then re-assess
  - Bedrest x 24h post infusion then re-assess
  - Maintain BP < 180/110 mm Hg if clinical deterioration,
    1. Discontinue tPA infusion
    2. Immediate CT scan
    3. Consider giving cryoprecipitate and platelets
  - Repeat CT scan after 24h in all cases
  - No IV heparin or ASA for 24h and repeat CT scan, ASA and/or heparin may be started after this period if the repeat CT scan is free of hemorrhage
  - At 45 minutes into the infusion, check tongue, lips for evidence of angioedema. If present, consider discontinuing tPA and administration of antihistaminergic and corticosteroids

---

**Inclusion Criteria**
- Acute ischemic stroke with clearly definable time of onset
- Patient presenting early enough so that thrombolytic infusion may be started within 3 hours from symptom onset

**Absolute Contraindications**
- TIA or stroke with rapidly improving deficit
- History and examination compatible with subarachnoid hemorrhage
- BP > 185/110 mm Hg after 2 attempts to reduce BP to this level
- Pre-treatment CT scan showing hemorrhage, mass effect or edema, tumour, or AVM
- Major surgery or trauma in the last 14 days
- Active internal bleeding
- Arterial puncture at a non-compressible site in the last 7 days
- History of hematological abnormality or coagulopathy, OR anticoagulation for any reason (PT > 15sec, INR > 1.4, PTT > 40sec, platelets <100 x 10^9/L)

**Relative Contraindications**
- Decreased level of consciousness
- CT scan showing a large area of early infarct changes
- Intracranial surgery or intraspinal surgery < 2 months
- Stroke or head injury in the preceding 3 months
- History of CI or GU hemorrhage in the preceding 21 days
- Previous history of central nervous system bleeding
- Glucose < 2.7 mmol/L or > 22.2 mmol/L
- Seizure at stroke onset
- Pregnancy
- Endocarditis, acute pericarditis
- Serious underlying medical illness, including liver failure

---

Fig. 2: Front (left) and back (right) of pocket-size card distributed to all members of the Department of Neurosciences and the Department of Emergency Medicine, Foothills Medical Centre, Calgary, for the intravenous administration of tPA. CBC = complete blood count, PT = prothrombin time, PTT = partial thromboplastin time, ECG = electrocardiography, IV = intravenous, BP = blood pressure, NIHSS = National Institutes of Health Stroke Scale, CNS = Canadian Neurological Scale, NPO = nothing by mouth, TIA = transient ischemic attack, AVM = arteriovenous malformation, INR = international normalized ratio, GI = gastrointestinal, GU = genitourinary.
lected over the third year of the program suggests that the main reason for not treating more patients is that either they do not arrive at hospital in time, or the time of symptom onset cannot be established reliably. Thrombolytic therapy will have little effect on stroke from a population standpoint if only 6% of patients can be treated. Since community surveys have shown that a substantial number of people cannot name even one symptom of stroke, public education about the symptoms and what to do about stroke can only increase the number of patients eligible for treatment.

The time from onset of symptoms to treatment is important. Animal data suggest that late reperfusion results in higher rates of hemorrhagic conversion. Treatment 3 to 6 hours after stroke onset is associated with a higher rate of symptomatic intracerebral hemorrhage than treatment before 3 hours. Under 3 hours, the time from symptom onset to treatment is not predictive of hemorrhage. However, patients who have early recanalization may have better outcomes. Our experience with EMS suggests that if the public can be taught to recognize stroke and react by calling 911, EMS will get them to the hospital promptly. The only limit can be taught to recognize stroke and react by calling 911, EMS will get them to the hospital promptly. The only limit.

The incremental improvements in treatment times over the study period suggest that there is a significant learning curve associated with the intravenous use of tPA for acute ischemic stroke. We are sobered by the fact that the improvement overall was gained primarily because patients reached the hospital faster. A major focus must now be on reducing the times from arrival to CT and from CT to treatment. The former can be as short as 5 minutes, which suggests that a target time of 30 minutes is both possible and reasonable. Neurologists took almost 1 hour to make the decision to start treatment. The fact that there was no improvement in CT-to-treatment times suggests that neurologists remain extremely cautious. This time is the most amenable to large improvement. With increased experience, it should be possible to meet this target.

We wish to acknowledge the following people, who were instrumental in the building of this program: (1) the members of the Neurology Department who treated the patients: Thomas E. Feasby (Chair, Department of Clinical Neurosciences), Werner J. Becker (Chair, Division of Neurology), Robert B. Bell, A. Keith W. Brownell, William A. Fletcher, Peter A.J. Forsyth, Neil A. Hagen, Keith Hoyte, Gary Klein, Anne-Louise LaFontaine, Mary Anne Lee, Robert G. Lee, Scott K. Meckling, Luanne M. Metz, William F. Murphy, David G. Patry, Chris Power, Neelan Pillay, Ranjit N. Ranawaya, Oksana Suchowsky, Chris M. White and Douglas W. Zochodne; (2) John A. King and the Calgary Regional Health Authority for funding the program and tissue plasminogen activator; (3) Robert Johnston and Robert J. Abernethy from the Emergency Department; (4) Willie Hu, Mark Hudson, Carla Wallace, T. Chen Fong and James Scott from the Foothills Diagnostic Imaging Department; (5) Jean Rankin from the Department of Nursing; and (6) Steve Long from the Department of Pharmacy.

Dr. Hill is supported by a joint Fellowship Award from the Heart and Stroke Foundation of Canada and the Medical Research Council of Canada, and in part by an Alberta Heritage Foundation for Medical Research Incentive Award. Dr. Buchanan is supported by grants from the Heart and Stroke Foundation of Alberta/North West Territories, the Medical Research Council of Canada and the Alberta Heritage Foundation for Medical Research.

Competing interests: None for Dr. Sevick, Ms. Newcommon and Ms. Green. Drs. Hill, Demchuk and Buchanan have received speaker fees from Hoffmann-La Roche Canada Inc. Dr. Barber has received travel assistance from Knoll Pharma Inc.

References


Reprint requests to: Dr. Michael D. Hill, Stroke Research Office, Foothills Medical Centre, 1403–29th St. NW, Calgary AB T2N 2T9; fax 403 670-1602; michael.hill@chfa-health.ab.ca

CMAJ • MAY 30, 2000; 162 (11) 1593