Stroke thrombolysis: Is tissue plasminogen activator a defibrillator for the brain?

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> It is in the nature of a stroke to paralyze a man and to throw him on the parish if he has no relatives to look to.
> — George Eliot, *Silas Marner*

The announcement on Feb. 17, 1999, of the Health Protection Branch's approval of Activase® rt-PA, a tissue plasminogen activator (tPA), now moves acute stroke into an era of therapeutic optimism and away from the nihilism that has too long characterized this "Cinderella" specialty. Although tPA is reserved for only a fraction of patients presenting with ischemic stroke, as with the advent of defibrillators to treat cardiac arrest, it is likely to be the first step in a sequence of advances that will revolutionize our understanding and approach to stroke therapy.

The problem with stroke is the rapidity of the pathological process; simply stated, it is "apoplectic." Within seconds of cerebrovascular occlusion, neurons depolarize, which results in an abrupt onset of symptoms such as paralysis and aphasia. This depolarization opens ion channels, resulting in a massive influx of calcium, and within minutes of inadequate blood flow the brain parenchyma is put at risk of irreversible infarction. A trial by the National Institute of Neurological Disorders and Stroke (NINDS)[1] confirmed data from animal models, showing that reperfusion can be clinically beneficial, but only if thrombolytic therapy is administered within 3 hours after symptom onset. The Second European–Australasian Acute Stroke Study (ECASS II)[2] failed to show that the window for tPA therapy may be extended to 6 hours after onset.[2] Neuroprotective drugs, which block calcium fluxes and prevent excitotoxicity, may one day extend the 3-hour window for tPA treatment by bestowing ischemic tolerance.[3] Although effective in animal models, none of these neuroprotective agents has been proven successful in a phase III trial.[4]

Although tPA is now approved for use in Canada, questions remain about its effectiveness and safety in the community. Physicians treating stroke patients must learn how to optimize the delivery of thrombolytic therapy. How do we pick patients who are most likely to benefit? How do we reduce the risk of or avoid incurring hemorrhage when it is unlikely that the patient will respond?

In the NINDS trial[1] 42% of the patients who received tPA had made an independent recovery at 3 months' follow-up, as compared with only 26% of those who received placebo. This 16% absolute risk reduction was highly significant. Although the primary analysis of ECASS II showed a statistically nonsignificant result (40.3% of those treated and 36.6% of the control group made a complete recovery), a secondary analysis of "independent recovery" revealed a significant 8% difference despite patients being treated up to 6 hours after symptom onset. The NINDS data showed that the number needed to treat (NNT) to generate one additional independent recovery was 6. In comparison, treatment with ASA in the International Stroke Trial showed that 111 stroke patients would have to be treated with 300 mg of ASA to prevent one death or recurrent stroke.[5] The NNT of 6 compares favourably with that achieved by performing a carotid endarterectomy for symptomatic ipsilateral stenosis of 70% of greater (NNT = 8 over 2 years).[6] The NNT with anticoagulant therapy in patients with atrial fibrillation would be about 32,[7] whereas with endarterectomy for asymptomatic stenosis it would be 67.[8] The NNT with ASA prophylaxis for 1 year in patients with transient ischemic attack would be 50.[9] Substitution from ASA to the newly launched antiplatelet agent, clopidogrel, has an NNT of 196.[10]

The main concern with tPA therapy for stroke is the increased risk of intracerebral hemorrhage. In the NINDS study the risk of symptomatic hemorrhage rose from about 1% without treatment to 6%.[1] In the ECASS II study it rose from 3.4% to 8.8%.[2] Subsequently, retrospective attempts have been made to identify patients at high risk for hemorrhagic complications. Factors that increase risk are increasing age,[1] uncontrolled hypertension,[1] severity of the stroke,[1] elevated blood glucose levels[11] and evidence of a large infarct in the middle cerebral artery on a CT scan done immediately before thrombolysis.[2] The risk of hemorrhage from tPA remains at about 6%, which is comparable to the accepted risk of stroke or death from endarterectomy (5%). These risk rates are determined from carefully controlled clinical trials, in which either selected surgeons were chosen because of their low surgical morbidity and mortality rates,[6,8] or by trained investigators participating in randomized trials of tPA for acute stroke.[1,2] However, can the results of major controlled clinical trials be translated into safe and effective care in routine practice?[12] As with complication rates of carotid endarterectomy, maintaining low hemorrhage rates among patients receiving tPA in the community will depend on appropriate patient selection and prospective audit.

In Calgary we now have experience of treating more than 100 consecutive patients with intravenous tPA therapy within 3 hours of stroke and have recently reported the 3-month outcome for the first 68.[13] Fifty-seven of those patients adhered to the NINDS protocol: at 3 months' follow-up although 3 (5%) had suffered a symptomatic hemorrhage and 6 (10%) had died, 38 (67%) had made an independent recovery. We concluded that this therapy was effective in a community setting. The stroke team was keenly aware that, when therapy is translated into practice, guidelines[14] (derived from the original protocol[1]) will occasionally be breached. In the subset of 11 patients who did not strictly adhere to the protocol, we were unable to demonstrate any positive outcomes, and these patients carried excessive risk.[13]

Physicians will have to decide within their own hospitals and communities whether tPA therapy can be delivered effectively and safely. To do this requires a contemporary awareness of stroke, funding by provincial and regional health authorities, and restructuring of existing neurological services. Given that less than 20% of patients with stroke reach hospital in a timely fashion, the first priority must be the education of those at risk so that they recognize the symptoms of stroke and know how and when to react. Emergency medical service (EMS) personnel need to be organized to triage stroke with the same priority as cardiac arrest and life-threatening trauma. For years stroke has been called the "Humpty Dumpty" syndrome ("all the King's horses and all the King's men couldn't put Humpty together again"). With the acceptance of tPA as a treatment for stroke, ambulance and EMS personnel must put systems in place to move the right patients to the right place as fast as possible. Stroke centres must now be designated in major metropolitan areas, with stroke teams trained and available to organize the immediate care of these patients in order to ensure that potential candidates for thrombolysis are screened within minutes of their arrival at the hospital. These centres must extend outreach support to smaller communities and expedite transfer or, if more appropriate, provide necessary support to make tPA therapy available in rural centres with CT scanning. CT services will need to be made available on a 24-hour basis, and those knowledgeable in the interpretation of early ischemic changes on CT scans will need to be consulted.[15] Protocols will have to be in place[14] and *strictly* adhered to if the risk is to be minimized.[13] Neurologists or physicians interested in stroke will need to be on hand[16] to identify patients who conform to the guidelines and to interpret the CT scans. Hospitals will need to make resources available for stroke teams. To facilitate and optimize care, stroke treatment units should be created in the same way as coronary care units, where monitoring systems and defibrillators became part of clinical practice in the 1960s.

A widely available, effective therapy for stroke would cap the neuroscience research efforts of the "decade of the brain" and would indeed be cause for celebration.[17]

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