THROMBOLYTIC THERAPY FOR ACUTE ISCHEMIC STROKE

The CAEP Position Statement: another perspective

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The cautiously-worded Position Statement recently issued by the Canadian Association of Emergency Physicians (see Appendix 1) regarding the use of intravenous recombinant tissue-plasminogen activator (tPA, alteplase) for acute ischemic stroke[1] underscores the reality that many physicians in Canada have been reluctant to embrace this therapy. Much of the caution expressed in the CAEP document is related to 2 major areas of concern: evidence of efficacy (i.e., did tPA really "prove" itself in randomized trials?) and effectiveness (i.e., are the trial results generalizable to everyday practice?). While we support the development of documents that help to clarify controversial treatments, and agree with much of what is presented in the CAEP Position Statement, we offer the following comments.

The best evidence of efficacy comes from systematic reviews of all of the available randomized controlled trials. Unfortunately, the CAEP position paper focused on individual trial results, which, although informative, can be misleading — especially if taken out of context. The CAEP document overlooks the Cochrane Collaboration Systematic Review of thrombolysis for acute ischemic stroke,[2] a peer-reviewed, systematically-developed, up-to-date summary and meta-analysis of the evidence from all of the randomized trials of tPA for acute ischemic stroke. The most recent version of the systematic review includes information from 8 randomized controlled trials of 2889 patients treated with tPA. The data clearly show that the risk of intracranial hemorrhage (ICH) with the use of tPA is offset by improvements in long-term outcome. Even after taking into account the occurrence of ICH, those patients receiving tPA within 3 hours of symptom onset experienced a statistically significant and clinically important 12.5% reduction in the absolute risk of long-term dependence or death (95% confidence interval [CI], 6.1%–18.9%; number needed to treat [NNT] = 8; 95% CI, 5–16). Expressed differently, this means that for every 1000 patients treated with tPA within 3 hours of symptom onset, an additional 125 patients (95% CI, 63–200) could avoid death or dependency (compared with placebo). Although some have suggested that tPA offers only a modest treatment effect, the NNT for tPA within 3 hours compares favourably with both carotid endarterectomy (NNT = 6 for symptomatic stenosis >70%, and an accepted morbidity and mortality of 6%) and thrombolysis for myocardial infarction (NNT = 26, or an additional 39 lives saved for every 1000 patients treated, and accepted morbidity and mortality of 1%).[3,4] We recognize that the observations from the systematic review are based on an analysis of relatively small numbers of patients, but they represent the best randomized data that we have at present and are well supported by the accumulated evidence of the overall effectiveness of tPA in Canada.

The most relevant evidence of the *effectiveness* of tPA for acute ischemic stroke comes from the Canadian Activase for Stroke Effectiveness Study (CASES).[5] This is a post-marketing surveillance study that was mandated by Health Canada in February 1999 when tPA was conditionally approved for the treatment of patients within 3 hours of onset of an ischemic stroke. All physicians who treat a stroke patient with tPA in Canada have been asked to submit information about the patient, the stroke (including pre- and post-treatment CT scans), and the outcome (in hospital and at 3 months) to the CASES Coordinating Centre in the Department of Clinical Neurosciences at the Foothills Hospital in Calgary. To date, 850 patients have been reported from

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Received: Mar. 07, 2001; accepted: Mar. 21, 2001.

25 teaching hospitals and 31 community hospitals from coast to coast, making this the largest post-marketing surveillance study of tPA in the world. Only 14% of patients have been treated in violation of the treatment protocol, whereas 33% of patients in the US post-marketing surveillance study (STARS) were protocol violators.[6] Symptomatic ICH has occurred in 41 CASES patients (4.9%, 95% CI 3.5%–6.5%), which compares favourably with the rate of 6.4% reported in the tPA-treated group in the NINDS rtPA Stroke Study.[7] Neurological outcome among the CASES patients is similar to that of the tPA-treated patients included in the Cochrane Systematic Review. In other words, Canadian physicians in a variety of practice settings have demonstrated that they can execute a difficult protocol and obtain outcomes that are commensurate with those reported from rigorous clinical trials. These findings were presented in 2000 at the national meetings of the Canadian Association of Emergency Physicians (CAEP), the Canadian Congress of Neurological Sciences, the Royal College of Physicians and Surgeons of Canada and the Canadian Cardiovascular Society,[8–11] as well as at other international meetings and symposia. The CASES study will complete enrollment on June 30, 2001, and final results should be available by year's end.

The results of tPA treatment for ischemic stroke in Cleveland, Ohio,[12] have been cited frequently by those who doubt the effectiveness and safety of stroke thrombolysis. Given the narrow therapeutic index for stroke thrombolysis, it would be surprising if a negative experience with intravenous tPA had not surfaced. The paper in question, however, reported a series of only 70 patients; there was evidence of poor patient selection (50% were protocol violators), a low level of experience (few centres had treated more than 5 patients annually) and a comparison group that did exceedingly well. The implication is that selection bias may have played a role in the reported outcomes.

We are encouraged by the totality of the data and believe that they are grounds for the wider deployment of thrombolytic treatment for stroke. While caution is prudent because tPA is expensive and potentially dangerous, we are concerned that CAEP's position is too restrictive and that some patients will be denied access to a therapy from which they stand to benefit.

For example, the Position Statement recommends that "Only radiologists or neurologists with demonstrated expertise in neuroradiology should provide interpretation of CT scans…", yet the identification of the important features is not so complicated that it cannot be learned by motivated emergency physicians or internists, perhaps by using the Alberta Stroke Program Early CT Score (ASPECTS) — a semi-quantitative structured approach to CT scan interpretation.[12] The meaning of early ischemic changes on CT remains controversial and are the subject of ongoing research. Early changes of ischemia on the baseline CT were *not* an exclusion criterion in the NINDS rtPA Stroke Study, which remains the basis for licensure in Canada.

Similarly, CAEP's recommendation that "Neurologists should be directly involved prior to the administration of thrombolytic therapy" does nothing to encourage emergency physicians and internists — who have the greatest collective experience in the assessment of acute stroke patients in this country — to take the few steps necessary to upgrade their skills in order to be able to effectively administer tPA.

We are reminded of the situation when thrombolytic agents were introduced for the treatment of acute myocardial infarction (MI). Some of the earliest Ontario Medical Association guidelines for acute MI[13] stated: "To avoid delays caused by transfer of patients, use of thrombolytic agents cannot be confined to large hospitals with invasive or operative facilities" and "any hospital that accepts responsibility for looking after patients with acute myocardial infarction could offer thrombolytic therapy."

It cannot be emphasized enough that the use of tPA is one small part of the appropriate care for people with stroke. Most patients presenting with an acute ischemic stroke will not be eligible for tPA. The vast majority, however, will benefit from organized care provided by multidisciplinary teams on geographically defined stroke units — an approach that has been shown to yield an additional 70 patients alive and independent for every 1000 admitted (NNT = 18).[14] Another lesson from the cardiologists is that improved organization of services will also provide the infrastructure to facilitate the conduct of large randomized trials of new treatments for stroke.

We agree with CAEP that it is unreasonable to advocate the use of tPA in centres that cannot provide access to stroke unit care thereafter. It is clear that the organization of stroke services needs to be improved in many parts of the country. Indeed, the Canadian Stroke Systems Coalition (of which CAEP is a member organization) was formed in response to the many challenges posed by the advent of thrombolytic therapy.[15]

There simply are not enough neurologists in Canada — now, or in the foreseeable future — to manage every acute stroke patient. Emergency physicians will continue to play a key role. We need to work together to improve the lot of those who suffer a stroke. Steps have already been taken toward this goal: a multidisciplinary group (including rep-

resentation from CAEP, the neurological community and others) has been formed to develop revised guidelines for stroke thrombolysis in Canada.

Financial disclosure: Dr. Phillips has received honoraria from Hoffmann La–Roche through participation in advisory panels, CME speaking engagements and the Canadian Activase for Stroke Effectiveness Study. Drs. Buchan and Hill have received honoraria for speaking at educational symposia in 1999 and 2000 for Hoffmann La–Roche Canada Ltd.

Acknowledgements: Dr. Hill was supported in part by the Canadian Institutes for Health Research, the Heart and Stroke Foundation of Canada, and the Alberta Heritage Foundation for Medical Research. Dr. Buchan was supported in part by the Heart and Stroke Foundation of Alberta/NWT, and the Alberta Heritage Foundation for Medical Research.

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Appendix 1. Recommendations from the CAEP Position Statement on thrombolytic therapy for acute ischemic stroke

The Canadian Association of Emergency Physicians enthusiastically endorses the promotion of stroke therapies when the benefits clearly outweigh the risks. These include the use of ASA, prevention of aspiration, early rehabilitation, and the establishment of stroke units and protocols. It is the position of the Canadian Association of Emergency Physicians that thrombolytic therapy for acute stroke should be restricted to use in the context of formal research protocols, or in closely monitored programs, until there is further evidence that the benefits of this therapy clearly outweigh the risks. All outcome data should be collated and made available to the medical community. It is important that studies of the safety and effectiveness of this th erapy be carried out in community hospitals.

Recommendation #1: Only radiologists or neurologists with demonstrated expertise in neuroradiology should provide interpretation of CT scans of the head used for the purpose of deciding whether to administer thrombolytic agents to stroke patients.

Recommendation #2: Stroke thrombolysis should be limited to centres with appropriate neurological and neuro-imaging resources that are capable of administering this therapy within 3 hours. In such centres, emergency physicians should identify potential candidates, initiate low risk interventions and facilitate prompt CT scanning. They should not be the primary decision-makers concerning the administration of thrombolytic agents to stroke patients. Neurologists should be directly involved prior to the administration of thrombolytic therapy.

Recommendation #3: Administration of thrombolytic agents to stroke patients should be carried out only in the setting of an approved research protocol or a formal clinical practice protocol. These protocols should adhere to the NINDS eligibility criteria. All data on adherence to protocols and patient outcomes should be collated in a central Canadian registry for the purposes of tracking the safety and efficacy of this intervention.

Adapted from CAEP Committee on Thrombolytic Therapy for Acute Ischemic Stroke. Thrombolytic therapy for acute ischemic stroke [position statement]. CJEM 2001;3(1):8-12.