

Canadian Guidelines for Intravenous Thrombolytic Treatment in Acute Stroke

A Consensus Statement of The Canadian Stroke Consortium

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ABSTRACT: Background: The thrombolytic drug, tissue plasminogen activator (tPA) has been approved in the United States for the treatment of acute ischemic stroke amid controversy and concern about the balance of risk and benefit. The Canadian Stroke Consortium (CSC), a national network of neurologists who collaborate on joint projects in stroke medicine, including clinical trials and consensus statements, has developed guidelines for the use of tPA in Canada. **Methods and Results:** The CSC Board of Directors wrote a preliminary report based on existing publications, including randomized drug trials and the report of a special committee struck by the Stroke Council of the American Heart Association. This draft was circulated to the CSC membership-at-large for suggestions or amendments, to produce this final draft. **Conclusions:** The present guidelines have been devised to represent a Canadian viewpoint of management. The Health Protection Branch of the Ministry of Health of Canada has not yet produced an evaluation. Further modification of these guidelines may be necessary when more data from clinical trials and experience with the drug become available.

RÉSUMÉ: Lignes directrices canadiennes pour la thrombolyse intraveineuse dans l'AVC aigu. Introduction: L'activateur du plasminogène tissulaire (tPA), un médicament thrombolytique, a été approuvé pour le traitement de l'accident vasculaire cérébral (AVC) aigu aux États-Unis, malgré la controverse et l'inquiétude concernant l'équilibre entre les risques et les bénéfices de ce traitement. Le consortium canadien sur l'AVC (CCAVC), un réseau national de neurologues qui collaborent à des projets conjoints en médecine de l'AVC, incluant les essais thérapeutiques et les déclarations de consensus, a développé des lignes directrices pour l'utilisation du tPA au Canada. **Méthodes et résultats:** Le conseil d'administration du CCAVC a émis un rapport préliminaire basé sur la littérature concernant les essais thérapeutiques randomisés et le rapport d'un comité spécial émis par le Stroke Council de l'American Heart Association. Ce document préliminaire a été distribué à tous les membres du CCAVC pour consultation en vue de la version finale. **Conclusions:** Les lignes directrices actuelles ont été élaborées pour refléter le point de vue canadien sur le traitement. La DGPS de Santé Canada n'a pas encore évalué le document. Il sera peut-être nécessaire de modifier ces lignes directrices à la lumière de nouvelles données provenant d'essais thérapeutiques et de l'utilisation du médicament en pratique courante.

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Caution: The following statement should not be considered an endorsement for the general use of t-PA in acute ischemic stroke. When deemed indicated, t-PA should be used solely by physicians experienced in acute stroke management.

Between 1995 - 1996, results of five randomized, placebo controlled trials of intravenous thrombolysis were published, using either streptokinase or recombinant tissue plasminogen activator, t-PA.¹⁻⁵ Trials of intra-arterial thrombolytic agents are still in progress and will not be dealt with here.

The FDA approved t-PA for clinical use in June 1996. However, there is concern that the use of t-PA, without proper safeguards, may result in net harm, in acute stroke patients. The Canadian Stroke Consortium has drafted this consensus statement, based on current available evidence and with reference to the Stroke Council of the American Heart Association (AHA) published guidelines.⁶

The role of t-PA for acute ischemic stroke remains controversial.⁷ We recommend that its use be restricted to physicians who are experienced in the management of acute stroke and who work in hospitals where the protocol has been approved, for those patients who fall within the strict guidelines we outline and with the understanding that it may confer benefit and that it does carry significant risk. The patient and family need to be fully informed. Modification of these guidelines is likely with the publication of additional trials currently in progress.

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SUMMARIES OF RECENT TRIALS

Streptokinase Trials

There have been three trials of intravenous streptokinase: multicentre acute stroke trials - MAST E (Europe)¹ and MAST I (Italy),² and the Australian Streptokinase Trial (ASK).³ All were stopped by the Safety Committees because of increased mortality and increased cerebral hemorrhage. At present, streptokinase cannot be recommended except as part of a clinical trial.

t-PA Trials

There have been two trials, the European Cooperative Acute Stroke Study (ECASS)⁴ and the National Institute of Neurological Disorders and Stroke (NINDS) Study.⁵

In the ECASS study, t-PA was given I.V. at a dose of 1.1 mg/kg up to a total of 100 mg, infusing 10% over 1-2 minutes and the rest over the next hour. There was no significant effect on neurological recovery and a non-significant increase in mortality. Intracranial hemorrhages were three fold more common than in the control group. The time window in this study was 6 hours.

In the NINDS study, t-PA was given at a dose of 0.9 mg/kg up to a total of 90 mg, again infusing over one hour. Although there was no significant difference in mortality at 3 months, there was significantly less disability in the t-PA treated group while symptomatic intracranial hemorrhage was 10 fold more frequent in the t-PA treated group (6.4% vs. 0.6%). The time window was 3 hours.

A recent systematic review of these trials has stated that there is insufficient evidence to recommend the use of thrombolytic drugs to treat acute ischemic stroke at the moment except in the context of further randomized controlled trials.⁸

Guidelines

- 1) Thrombolytic therapy for acute stroke must be administered in an acute care setting by a physician with expertise in the diagnosis and management of stroke. In most cases t-PA will be given by a neurologist in a tertiary care or major hospital setting. The use of a hospital-approved protocol is recommended. Community hospitals considering the use of t-PA should assess their capability to accurately and safely apply these guidelines.
- 2) CT scanning must be available on a 24 hour basis with personnel experienced in the detection of early CT signs of significant infarction and intracerebral hemorrhage. CT evidence of cerebral hemorrhage or significant mass effect, as shown by ventricular compression or midline shift, are absolute contra-indications to thrombolytic therapy. Early signs of ischemia including sulcal effacement or parenchymal hypodensity are associated with an increased risk of intracranial bleeding but are not absolute contra-indications to t-PA.
- 3) t-PA should be administered intravenously in a dose of 0.9 mg/kg to a maximum of 90 mg, with an initial 10% given as a bolus over 1-2 minutes and the remainder of the dose infused over 60 minutes. The drug must be given within 3 hours of stroke onset. It is not recommended if the time of symptom onset is uncertain, for example in aphasic patients without collateral history or in patients who have neurological deficits upon awakening.

4) Exclusions:

- i) CT evidence of cerebral hemorrhage or an infarction involving more than one-third of middle cerebral artery territory
 - ii) Blood pressure > 185/110
 - iii) Use of anticoagulants in the previous 48 hours and a prolonged PTT or an INR > 1.7 or platelet count < 100,000
 - iv) Stroke or head injury in the prior 3 months
 - v) Major surgery within prior 14 days
 - vi) Blood glucose < 3 or > 22 mmol/L
 - vii) Seizures at the onset of stroke
 - viii) Other bleeding (e.g., G.I.) within prior 21 days
 - ix) Myocardial infarct within 3 weeks
 - x) Rapidly improving neurological signs or minimal deficit
 - xi) Other illness that could limit effectiveness or increase risk of bleeding in the judgment of the physician.
- 5) No aspirin, heparin, warfarin, ticlopidine or other antiplatelet drugs must be given for at least 24 hours after t-PA. Aspirin treatment prior to t-PA infusion is not a contra-indication.
 - 6) Facilities must be readily available on a 24 hour basis to manage hemorrhagic complications. Intracerebral hemorrhage is probable if unexpected neurological deterioration occurs following the use of t-PA. The infusion should be discontinued immediately and an emergency CT scan obtained. The indications for neurosurgical intervention have not been defined for either spontaneous intracerebral hematomas or those associated with t-PA treatment. Management decisions have to be made empirically by the responsible physician with or without consultation with a neurosurgeon.
 - 7) Vital signs should be taken every 15 minutes during the drug infusion, then 30 minutes for the next 2 hours, then hourly for 5 hours. Neurovital signs should be performed hourly for 6 hours, and then according to the patient's condition.
 - 8) If patient is hypertensive (BP > 180/110), labetalol should be infused I.V. 10 mg over 1-2 minutes repeated every 10-20 minutes up to a dose of 150 mg. Monitoring the BP every 15 minutes during and for 24 hours after t-PA has been given.⁶
 - 9) Informed consent should be obtained from the patient and/or family prior to treatment with t-PA in accordance with hospital policies and procedures.

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