Thrombolytic Therapy in Acute Ischaemic Stroke
Do the Benefits Outweigh the Risks?

Geoffrey A. Donnan¹ and Stephen M. Davis²

1 Department of Neurology, Austin and Repatriation Medical Centre, University of Melbourne, Heidelberg, Victoria, Australia
2 Department of Neurology, Royal Melbourne Hospital, Melbourne, Victoria, Australia

Summary

There is a body of experimental and anecdotal evidence to suggest that thrombolytic therapy may be useful in reducing morbidity and mortality after acute ischaemic stroke. A series of clinical trials designed to test hypotheses concerning risk and benefit have now been published. Intravenous streptokinase when given within 6 hours of ischaemic stroke may be of marginal benefit when given alone, but of no benefit when given with aspirin (acetylsalicylic acid) because of an unacceptably high early mortality. There is a trend toward much better outcomes if streptokinase is given early (<3 hours post-stroke). Intravenous alteplase (tissue plasminogen activator; tPA) has a much better risk-benefit profile than streptokinase, particularly when given within 3 hours of a stroke at a dose of 0.9 mg/kg. Indeed, this dose was recently approved for use by the US Food and Drug Administration.

Any planned administration of thrombolytic therapy to patients with acute ischaemic stroke should be in centres with experienced staff and facilities to monitor clinical progress. Further trials are needed to identify which thrombolytic agents, time windows of administration and dosages provide the best risk-benefit ratios.

The recent publication of a series of trials of thrombolytic agents in acute ischaemic stroke,¹¹⁵ and the positive results of some of these,¹³,⁴ has raised hopes that a form of medical therapy may at last be available to minimise the effects of cerebral ischaemia once it occurs. Stroke is the most common form of focal neurological disease in adults and the third most common cause of death in most countries. The social and economic impact of stroke is considerable, since most strokes do not result in death but cause persistent disability. Up to this time there has been no medical therapy to minimise the effects of acute stroke, but the introduction of new generation thrombolytic agents⁶,⁷ that have been shown to be effective in reducing morbidity and mortality after myocardial infarction⁸-¹⁰ has stimulated interest in similar forms of therapy for acute cerebral ischaemia.

In this article, we will briefly review the background to the issue of thrombolysis in ischaemic stroke and then review the recent major trials. There have been a number of earlier, smaller randomised controlled trials which will not be discussed in detail.
1. Recovery from Stroke: Arterial Recanalisation and Tissue Reperfusion

Since arterial thrombosis and embolism are the fundamental mechanisms by which most strokes occur,[11,12] thrombolytic therapy designed to recanalise recently occluded vessels is a logical therapeutic approach. This is supported by earlier clinical studies of cerebral infarction with initial and then repeated angiography.[13] These showed that occluded vessels may undergo spontaneous clot lysis, although in these cases there was no improvement in prognosis. However, single photon emission computerised tomography (SPECT) has shown that reperfusion at the tissue level is associated with better outcomes.[14]

Much of the improvement may be in underperfused areas where tissue remains viable, the so-called 'ischaemic penumbra'.[15] Electrical and synaptic failure occurs in this zone due to a reduction of blood flow to below a critical threshold. Further reduction of flow as a function of time leads to depletion of energy stores, membrane failure and subsequent infarction. However, the 'therapeutic window' of time available during which clot lysis with restoration of blood flow and recovery of neuronal function may occur is unclear.[11]

2. Thrombolytic Therapies

The introduction of fibrin-selective thrombolytic agents that have been shown to be well tolerated and effective in a number of thrombolytic disorders rekindled interest in similar forms of therapy for acute ischaemic stroke.[16] Experimental models of cerebral infarction have been used to show that thrombolytic agents such as alteplase [tissue plasminogen activator (tPA)], streptokinase and urokinase may cause clot lysis when given intra-arterially or intravenously and minimise the volume of infarction.[17] Alteplase has strong theoretical advantages because of its fibrin specificity and lack of other systemic thrombolytic effects[7] and, hence, has been the forerunner in trials of thrombolysis in cardiac disease. In these trials, alteplase has been shown to reduce mortality after myocardial infarction.[8-10] Streptokinase has also been shown to be equally effective in this role,[9] while agents such as prourokinase and recombinant staphylokinase remain to be tested.[18]

3. When Should Therapy Begin?

Although data from experimental models of cerebral ischaemia do suggest that neuronal recovery may still occur after 6 hours post-ischaemia,[19-21] this information is difficult to translate into the clinical sphere. While there are arguments to suggest that longer therapeutic time windows may exist in humans,[22] it seems logical that the earlier thrombolytic therapy is given, the greater the likelihood of success. This has been borne out in subsequent clinical trials and will be discussed in section 5.

4. Haemorrhagic Transformation

One of the main concerns regarding the use of thrombolytic agents in ischaemic stroke has been the potential to transform a 'bland' infarct into a cerebral haemorrhage with subsequent clinical deterioration. Such transformation may occur at multifocal sites via diapedesis through damaged capillary and venular walls, and results in petechiae of various sizes. Occasionally, confluence of petechiae results in confluent purpura or a haematoma. Cardiac embolic strokes have a higher propensity for haemorrhagic infarction (51 to 71% prevalence)[23,24] than non-cardiac embolic strokes (2 to 21% prevalence).[24,25] Haemorrhagic infarction may be detected on computed tomography (CT) scan, and is seen in up to 5% of scans performed within 24 hours of the stroke and up to 69% of cases when CT scan is performed within weeks post-stroke.[26-29] Although anticoagulant therapy does not appear to increase the likelihood of haemorrhagic transformation, it may accentuate the degree of frank haemorrhage on CT, with an estimated incidence of clinical deterioration of 5 to 20%.[30]