Thrombolytic therapy for acute ischaemic stroke

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Abstract

Thrombolytic therapy for acute ischaemic stroke improves outcome in a highly selected group of patients. It will shortly be licensed in the UK for this indication. Implementation of this treatment will be difficult as current stroke services are ill-equipped to meet the challenges associated with aggressive management of hyperacute stroke.

This article evaluates the published literature concerning thrombolytic therapy in the context of ischaemic stroke and briefly discuss the obstacles which prevent more widespread use of this treatment in the UK. It also considers the effect of age on efficacy and tolerability of thrombolytic therapy.

Key words: thrombolysis, stroke, elderly.

Br J Cardiol 2003;**10**:197–205

Introduction

Thrombolysis for stroke is not new but its current place in acute stroke management is reminiscent of thrombolysis for acute myocardial infarction (AMI) in 1984. It is hard to imagine that thrombolysis for myocardial infarction (MI) was once considered too risky, too likely to cause harm, and without benefit of a reduction in infarct size or effect on outcome. Reperfusion arrhythmias were a hot topic of research and clinical decision making.

Any doubts over thrombolysis in AMI were cast aside with the publication of the landmark Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto miocardico (GISSI) and Second International Study of Infarct Survival (ISIS-2) trials which transformed cardiology.[1,2] Almost overnight the administration of thrombolytic therapy by peripheral vein became standard treatment for AMI.

But what about thrombolytic therapy for acute ischaemic stroke? This article examines the emergence of data in this crucial area, and explains why stroke physicians are being cautious in their approach to thrombolysis for acute cerebral infarction.

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Stroke is a major public health issue. It is the leading cause of disability and the third leading cause of death (after heart disease and cancer) in the developed world,[3] where care of patients with stroke consumes approximately 7% of healthcare spending.

Although stroke may affect individuals of any age, it is primarily a disease of the elderly. The incidence of stroke rises sharply with age: almost one quarter of all strokes occur in those greater than 85 years old, and one half occur in those over 70 years. Age is an important predictor of outcome after stroke and there is growing evidence that elderly stroke survivors require more rehabilitation and are more likely to become dependant than younger survivors. The burden of stroke disease will rise in years to come due to the ageing UK population. To minimise this burden we have a great need for acute strategies and by far the most promising is thrombolytic therapy. This article reviews the role of intravenous thrombolysis for acute ischaemic stroke with particular consideration to its use in the older patient.

Lessons from cardiology

In the context of AMI, thrombolytic therapy reduces mortality and preserves left ventricular function.[2,3] It was hoped that intervention to reperfuse ischaemic brain would yield similar benefit. Ischaemic events account for approximately 85% of all strokes; about 60% of these are caused by vascular occlusion initiated in a local vessel, the majority of the remaining events arising as a consequence of embolism to the brain. It is believed that, like the process within coronary arteries, fibrinolytic drugs lyse the occluding thrombus with restoration of flow. Since arteries within the brain are end vessels without collaterals, the brain is much more easily damaged by small emboli or *in-situ* infarcts, whereas the coronary microcirculation has a rich network of collateral vessels.

Potential risks of thrombolysis are predictable from the pharmacology of thrombolytic drugs and the pathophysiology of cerebral ischaemia. Elderly patients, hypertensives and those with embolic stroke have a higher risk of spontaneous intracerebral haemorrhage, and may be at increased risk of bleeding following thrombolysis. Delay in treatment exposes the patient to a significant risk from complications without any prospect of benefit, as reperfusion of already irreversibly infarcted tissue increases the risk of haemorrhage. Cerebral reperfusion injury may occur when toxic free radicals are formed in an ischaemic area following re-oxygenation of profoundly ischaemic tissue. This process may lead to brain swelling and compression of other delicate intracranial structures, with deleterious consequences for the

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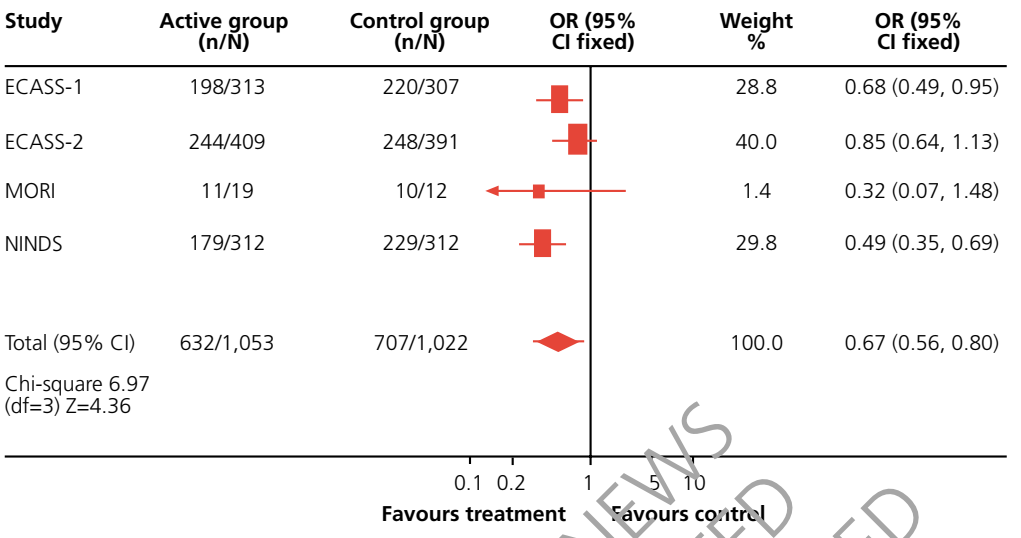
Figure 1. Effect of rt-PA on death and disability in the major trials. Comparison: thrombolysis versus placebo. Outcome: death and disability



Key: OR = PETO odds ratio; CI = confidence interval; rt-PA = recombinant tissue plasminogen activator

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patient. These factors were reflected in the design of clinical trials of thrombolysis for stroke.

Intravenous streptokinase studies

Three large multi-centre trials[4-6] have examined the effect of thrombolysis with streptokinase after ischaemic stroke. Excess early mortality was observed in the treated groups of all three trials, correlating with significantly higher rates of intracranial haemorrhage.

Meta-analysis of data accumulated from the streptokinase trials did not reveal factors which predisposed to early mortality. To date, no randomised controlled trial has supported the use of intravenous streptokinase in the context of acute ischaemic stroke. Further studies of streptokinase using different patient selection criteria, lower doses of thrombolytic and prohibition of antiplatelet or anticoagulant co-administration have been proposed – at present no such trial is underway. Although some debate remains,[7] it is unlikely that streptokinase will have a role in the management of acute ischaemic stroke.

Intravenous recombinant tissue plasminogen activator studies

Four major trials have evaluated the role of recombinant tissue plasminogen activator (rt-PA) in patients with acute stroke. Pharmacological characteristics of this agent are rather more favourable than those of streptokinase in the treatment of stroke patients – rt-PA is not antigenic and does not lower blood pressure (BP) during infusion. This may be significant since reducing BP immediately after ischaemic stroke has been associated with worse outcome.[8] Furthermore it causes less disruption of the coagulation cascade and is more 'clot specific'; comparatively fewer haemorrhagic complications may be observed.

The European Co-operative Acute Stroke Study (ECASS 1),[9] National Institute of Neurological Diseases and Stroke rt-PA Stroke Study (NINDS),[10] and ECASS 2[11] evaluated rt-PA at doses of 1.1 mg/kg, 0.9 mg/kg and 0.9 mg/kg respectively. Patients were treated within six hours in the ECASS studies and three hours in the NINDS study. Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischaemic Stroke (ATLANTIS) study[12] used a dose of 0.9 mg/kg administered within an initial time window of six hours; this window was later modified in the light of emergent evidence from the other rt-PA studies.

ECASS 1

Results of ECASS 1 are notable for the large proportion of patients excluded from the target population (TP) analysis (109 out of 620 randomised). The protocol intended to exclude patients with more than one third MCA territory stroke on computed tomography (CT) i.e. those with large areas of cerebral infarction. Sixty-six patients with ineligible CT scans were recruited; survival in protocol violators was significantly worse than for those meeting the entry criteria. TP analysis was positive, with a reported improvement in functional outcome at three months (p=0.03) but the intention to treat (ITT) analysis was negative. Mortality was non-significantly higher in the rt-PA group in both ITT and TP analysis.

NINDS

The NINDS Study investigated the potential benefit of a lower dose of rt-PA given within three hours of onset of symptoms. An improvement in functional outcome was seen at three months, with those in the treated group 30% more likely to have negligible disability than placebo recipients. No difference in mortality between groups was observed, although there was an

Table 1. Predictors of poor and good outcome following thrombolysis for stroke

Poor outcome
Hypertension
Diabetes mellitus
Evidence of early infarction on initial CT scan of brain
Large vessel (e.g. internal carotid artery) occlusion
Increasing age
Good outcome
Young patient
Minimal pre-existing disability
No parenchymal infarction on CT brain
Early administration within three hour time window

Key: CT = computed tomography

Table 2. Changes needed for thrombolysis to become widespread

- Increase in public awareness of acute brain attack, like acute heart attack
- Immediate access to MRI/CT imaging, like an ECG for acute MI
- A tight definition for general physicians indicating which patients will benefit from thrombolysis
- TIA to be redefined as resolution complete or near complete within one hour; more prolonged symptoms likely indicate evolving stroke

Key: MRI = magnetic resonance imaging; CT = computed tomography; ECG = electrocardiogram; MI = myocardial infarction; TIA = transient ischaemic attack

increase in symptomatic intracerebral haemorrhage 7% *vs.* 1% (rt-PA *vs.* placebo).

ECASS 2

The ECASS 2 investigators sought to extend the time window for thrombolysis to six hours, using the low dose of rt-PA used in the NINDS study. The study failed to demonstrate a statistically significant difference between treated and placebo groups; however retrospective analysis of the data, using a different threshold of Rankin score[13] to define a good outcome, suggested a beneficial effect of rt-PA. The authors concluded that rt-PA treatment leads to a clinically relevant improvement in outcome without increased morbidity and mortality despite increased symptomatic haemorrhage. The trial's failure to demonstrate efficacy using pre-determined end points, however, has led to its widespread interpretation as neutral.

ATLANTIS

The ATLANTIS study also investigated safety and efficacy of intravenous rt-PA 0.9 mg/kg within six hours of ischaemic stroke. Adverse interim safety analysis in the five to six-hour group lead to a truncation of the time window to five hours approximately two years after recruitment commenced. Following publication of the NINDS study in 1995, the time window was again changed (to three to five hours). The ATLANTIS study was terminated prematurely in July 1998 following a discouraging futility analysis. The 90-day results in the placebo and rt-PA groups did not differ with regard to the primary outcome measure. The use of intravenous rt-PA beyond three hours after stroke onset is not supported by the ATLANTIS study.

Effect of age on efficacy and tolerability of thrombolytic therapy

In the context of MI, thrombolytic therapy is associated with a higher risk of intracerebral haemorrhage when administered to the older patient.[14] Safety data from elderly stroke patients is sparse and conflicting as no trials have specifically addressed this issue and those over 80 years are under-represented in the major studies; indeed only 42 such patients have been studied in the rt-PA trials. In the NINDS trial[10] increasing age was not predictive of symptomatic intracerebral bleeding but elderly patients in both ECASS trials[9,11] were more likely to develop this complication.

Small post-marketing surveillance studies[15,16] suggest no significant differences in rates of intracerebral haemorrhage rates or outcome in older (> 80 years) recipients compared with younger patients, but numbers are too small to draw firm conclusions.

A number of factors may predispose the older patient to adverse events following thrombolysis. Cerebral amyloid angiopathy[17] and leukoaraiosis[18] are found more commonly and both may predispose to increased vascular frailty, and, hence, increase the risk of thrombolytic-related bleeding. In addition, reduced hepatic clearance of rt-PA in the elderly may potentiate and prolong thrombolytic activity,[19] hence increasing risk of haemorrhage.

Where do we go from here? Practical aspects and improved patient selection

There is some evidence to support the use of rt-PA in selected stroke patients if administered within three hours of the onset of symptoms within a specialised unit (see table 1). Results of a meta-analysis of the major rt-PA trials are shown in figure 1. Regulatory approval for implementation of this treatment in the UK is imminent. One large study[20] has suggested that translation of thrombolytic therapy from a clinical trial environment into routine practice is achievable in North America. Such a transition will prove more difficult in the UK (see table 2). Stroke is not widely perceived as a treatable condition, and the redefinition of stroke as an emergency will prove challenging. A further difficulty lies in the necessary provision of specialised stroke care, with out-of-hours access to appropriate brain imaging and the clinical expertise to manage these very ill and often unstable patients. The benefits of organised care for stroke patients are well recognised;[21] any acute strategies should be employed within such units. It is hoped that the advent of effective acute stroke therapies to complement existing strategies employed in stroke units

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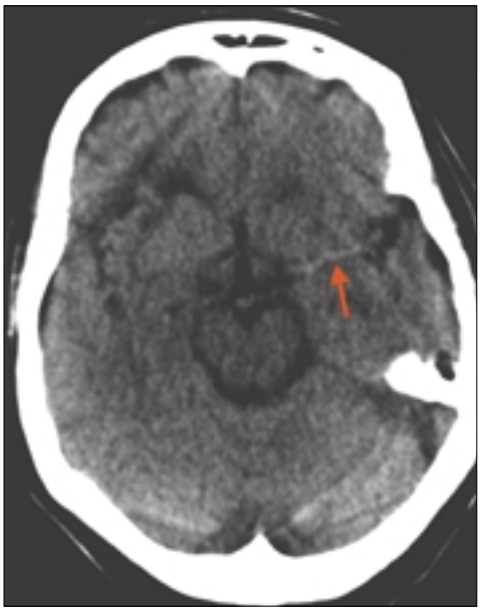
Figure 2. The 'dense MCA' sign of early hemispheric cerebral infarction



will stimulate an expansion in the numbers of such facilities in the UK. This will need to be coupled with new streamlined pathways of acute stroke care and substantial community education programmes if the potential benefits of thrombolysis for stroke are to be realised in practice.

A number of questions remain unanswered. We have insufficient data to assess the effects of stroke subtype or administration outside the three hour time window on the potential benefits of rt-PA. Similarly, it is unclear which patient characteristics or CT scan appearances (apart from large MCA infarct) may influence outcome. These uncertainties must be resolved, so that we can maximise benefit for patients while reducing risk.

At present, CT is used to exclude intracerebral haemorrhage prior to thrombolysis. This technique is more widely available than other imaging modalities, but it is highly unreliable in the detection of cerebral ischaemia. An example of the subtle nature of early CT changes following cerebral infarction is shown in figure 2. Multi-modal magnetic resonance imaging (mmMRI)[22] allows reliable identification, localisation and quantification of ischaemic core of the infarct using diffusion-weighted sequences (dwMRI), and evaluation of cerebral blood flow with perfusion weighted (pwMRI). Examination of the 'mismatch' between diffusion and perfusion deficit allows quantification of salvageable brain tissue and may improve patient selection for thrombolytic therapy.

Conclusion

Thrombolytic therapy has been evaluated in a number of clinical trials. There is some evidence that rt-PA may be beneficial if administered within three hours of onset of ischaemic stroke in a highly selected patient population. There is a higher risk of symptomatic and fatal intracerebral haemorrhage following thrombolysis but this is offset by less chance of death or dependency later. For now, administration of rt-PA should only be performed within specialist centres and few of these currently exist within the UK. The further evaluation of acute reperfusion strategies followed by the implementation of thrombolytic therapy in the clinical setting represents one of the most difficult but potentially rewarding challenges facing general physicians, neurologists and geriatricians today. Substantial changes in public awareness, including healthcare professionals will be required. Immediate access to MRI/CT imaging, is another major hurdle to overcome before thrombolysis for acute stroke becomes widespread.

Key messages

- Thrombolytic therapy is the only acute medical intervention shown to improve outcome after stroke
- It will shortly be licensed in the UK for this indication
- At present, only a small minority of patients are likely to benefit as treatment has to be administered within three hours of onset, and a CT scan is required within this tight time window
- Major changes in the public's perception of stroke and the provision of current stroke services will be required if thrombolysis is to be more widely used

Editors' note

This is the third article in our clinical cardiology series. Previous articles include:

- The future of cardiology: heart disease in older patients (*Br J Cardiol* 2003;**10**:45-8)
- Heart disease in older patients: myocardial infarction (*Br J Cardiol* 2003;**10**:123-7).

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