

Special Feature

An Update on Thrombolysis for Acute Ischaemic Stroke

Stroke is the third commonest cause of death and the leading cause of adult disability in the UK. Its burden is set to increase because of an ageing population. Recently the thrombolytic agent, recombinant tissue plasminogen activator (rt-PA/alteplase), received a licence for the treatment of acute ischaemic stroke, within three hours of symptom onset. It is the first thrombolytic agent to be licensed for this indication and has the potential to radically change the early management of acute ischaemic stroke and reduce resultant disability. However, its successful implementation poses a number of important challenges. This article provides an update on progress in this area.

Acute ischaemic stroke

Acute ischaemic stroke accounts for approximately 80% of all strokes, and occurs when a thrombus, or embolism, blocks a cerebral blood vessel. Resulting mortality and morbidity, particularly long term disability, are high. Approximately 20% of patients will die within thirty days of stroke onset, and many are left permanently disabled. Up to now treatment has been largely restricted to supportive and rehabilitative care. Organised stroke unit care, and the use of aspirin given as soon as possible after stroke onset, have been shown to offer benefit. However, no therapies that are able to reduce brain damage and resultant disability were available for immediate administration. This changed with the licensing of rt-PA in April 2003 in the UK.

Thrombolysis for acute ischaemic stroke

The two thrombolytic agents that have to date been most studied in stroke are recombinant tissue plasminogen activator (rt-PA) and streptokinase. The trials involving streptokinase have been disappointing, reporting an early increased risk of cerebral haemorrhage and death, with no net benefit at final follow-up¹. However, a number of large multicentre randomised placebo controlled trials have shown an overall benefit for early treatment with rt-PA, despite an increased risk of early haemorrhage^{2,3,4,5,6}. For example, the National Institute of Neurological Disorders and Stroke (NINDS) trial reported in 1995 that patients were at least 30% more likely to have minimal or no disability three months after their stroke if treated with rt-PA within three hours of symptom onset. Despite the risk of symptomatic intracranial haemorrhage, mortality at three months was lower in the rt-PA group at 17%, compared with 21% in the placebo group. More recently, pooled data from the six large randomised controlled trials of rt-PA, involving 2775 patients, was analysed to gain better insight into the effect of time to treatment on efficacy. The findings reported recently confirm that the sooner the treatment is given to suitable stroke patients, the greater the benefit⁷. The odds ratio for a favourable outcome at three months is shown below. These results con-

firm the strong association between rapid treatment and favourable outcome.

A Cochrane review of thrombolysis for acute ischaemic stroke analysed 18 randomised controlled trials of any thrombolytic agent⁸. The review included 5727 patients given urokinase, streptokinase, recombinant pro-urokinase or rt-PA. About half of the data comes from trials testing rt-PA. There is a paucity of data from patients aged >80 years. Overall thrombolytic therapy, administered up to 6 hours after ischaemic stroke, significantly reduced the proportion of patients who were dead or dependent (modified Rankin 3 – 6) at 3 to 6 months follow up. Overall the reviewers concluded that thrombolytic therapy appears to result in a significant net reduction in the proportion of patients dead or dependent in activities of daily living, despite an increase in early symptomatic intracranial haemorrhage or death. Further trials are underway to assess if benefit extends beyond the licensed 3-hour time window. The third International Stroke Trial (IST-3) is recruiting patients of all ages up to 6 hours after stroke. The third European Cooperative Acute Stroke Study (ECASS III) is examining potential benefit for patients in the 3-4 hour time window.

The use of rt-PA following stroke

rt-PA was licensed under the brand name Actilyse for use in acute ischaemic stroke in April 2003 in the UK. It must be administered within a 3-hour time window and was launched under strict licensing guidelines. Under these it can only be used by a physician specialised in acute stroke care and with experience in the use of thrombolytic treatments and appropriate facilities to monitor its use and complications. Brain imaging must be conducted before administration, to exclude intracranial haemorrhage or early signs of major infarction. Furthermore there is a requirement, as part of the licensing agreement, to register all treated patients within the Safe Implementation of Thrombolysis in Stroke MONitoring Study (SITS-MOST). This is an initiative by the medical profession to confirm that rt-PA remains a safe treatment choice outside of clinical trials. Details of the registry are available at www.acutestroke.org.

Observational studies

The Standard Treatment with Alteplase to Reverse Stroke (STARS) study suggested that favourable clinical outcomes and a low rate of symptomatic intracranial haemorrhage could be achieved⁹. Further experience has come from the Canadian Activase for Stroke Effectiveness Study (CASES). This study includes over 60 active centres in Canada and has presented results on 944 patients enrolled so far. Results to date indicate a lower rate of symptomatic intracranial haemorrhage (4.7%) than that found previously, even though the level of stroke severity is similar to the NINDS study (NIHSS



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Time to treatment administration (mins)	0-90	91 – 180	181 –271	271 – 360
Odds ratio for a favourable outcome	2.8 (CI 1.8-4.5)	1.6 (CI 1.1-2.2)	1.4 CI (1.1-1.9)	1.2 (0.9-1.5)

score = 15) with 30% of patients having minimal or no neurological deficit and 46% being independent at 90 days.

Potential barriers to delivery of thrombolysis

The safe introduction of thrombolytic therapy in the UK can only take place against the backdrop of an organised, efficient and integrated stroke service. However there are considerable logistical difficulties in organising services to enable thrombolysis to be delivered within the required 3-hour time window. A recent systematic review of this topic has been published and identified numerous barriers to thrombolysis¹⁰.

Meeting the required timeframe is only achievable alongside the promotion of rapid recognition of stroke symptoms by the public at large, public education about "brain attack" and a recognition that such patients require urgent transfer to hospital as quickly as possible and prompt access to specialised acute stroke units. Paramedics – the first point of contact for most patients with acute ischaemic stroke – have a vital role in the rapid recognition of stroke and transferring patients rapidly to hospital. Although many patients do arrive in the hospital within three hours of onset, unless they are triaged as high priority (much in the same way as those with acute heart attacks are) and managed quickly, thrombolysis is unlikely to have a major impact on outcome.

Conclusion

The benefits of thrombolysis using rt-PA within three hours of stroke onset can be substantial. By promoting the rapid recognition of stroke symptoms in the community, prompt transport of patients to specialised acute stroke units for early investigation, neuro-imaging, stabilisation and treatment, there would be substantial net benefit for all patients with stroke and not just for the small proportion (currently between 2.5% and 5%) eligible for thrombolysis. Clearly, we have a long way to go before "brain attack" is given the same degree of priority and urgency as "heart attack" currently is.

Barriers to thrombolysis

- failure of patient/carer to recognise the symptoms of stroke or seek urgent help
- initial contact with GP rather than ambulance
- failure of paramedical /emergency department staff to triage stroke as an emergency
- delays in neuro-imaging
- inefficient process of in-hospital emergency stroke care,
- difficulties in obtaining informed consent
- physician uncertainty in administering rt-PA.

Contraindications to thrombolysis with rt-PA:

Patients with:

- symptoms of ischaemic attack that began more than 3 hours prior to start of infusion or when time of symptom onset is unknown
- minor neurological deficit or symptoms that are

- rapidly improving before start of infusion
- severe stroke as assessed clinically (e.g. NIHSS>25) and/or by appropriate imaging techniques
- seizure at onset of stroke
- evidence of intracranial haemorrhage (ICH) on the CT scan
- symptoms suggestive of subarachnoid haemorrhage, even if the CT-scan is normal
- who have had heparin within the previous 48 hours and a thromboplastin time exceeding the upper limit of normal for laboratory
- any history of both prior stroke and concomitant diabetes
- a prior stroke within the last 3 months
- platelet count below 100,000/mm³
- systolic blood pressure >185mmHg or diastolic blood pressure >110mmHg or those on IV medication to reduce blood pressure to these limits
- blood glucose <2.8 or >22 mmol/l

Please refer to Actilyse Summary of Product Characteristics for a full list of contraindications.

References

1. Lees KR 2000 *Thrombolysis* British Medical Bulletin 56(2): 389-400.
2. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. 1995 *Tissue Plasminogen Activator for Acute Ischaemic Stroke* NEJM 333: 1581–1587.
3. Hacke E *et al* 1995 *Intravenous thrombolysis with recombinant tissue plasminogen activator for acute hemispheric stroke*. The European Cooperative Acute Stroke Study (ECASS) JAMA 274:1017-1025.
4. Hacke E *et al* 1998 *Randomised double-blind placebo-controlled trial of thrombolytic therapy with intravenous alteplase in acute ischaemic stroke (ECASS II)* Lancet 1998;352: 1245-1251.
5. Clark WM *et al* 2000 *The rt-PA (alteplase) 0 to 6 hour acute stroke trial, Part A (A0267g): Results of a double-blind, placebo-controlled multicentre study* Stroke 31: 811-816.
6. Clark WM *et al* 1999 *Recombinant tissue-type plasminogen activator (alteplase) for ischaemic stroke 3 to 5 hours after symptom onset: the ATLANTIS study: a randomised controlled trial* JAMA 282 (212):2019-2026.
7. Hacke W *et al* 2004 *Association of outcome with early stroke treatment: pooled analysis of ATLANTIS, ECASS and NINDS rt-PA stroke trials* Lancet 363(9411): 768-74.
8. Wardlaw JM *et al* 2004: *Thrombolysis for acute ischaemic stroke (Cochrane Review)*. Cochrane Library, Issue 1, 2004.
9. Albers GW *et al*. *Intravenous tissue-type plasminogen activator for treatment of acute stroke*. Journal of the American Medical Association 2000; 283:1145-50.
10. Kwan J *et al*. *A systematic review of barriers to delivery of thrombolysis for acute stroke*. Age and Ageing 2004; 33:116-121.

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