Thrombolysis for acute stroke in the United Kingdom

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Abstract

The publication of the National Institute of Neurological Disorders and Stroke trial of thrombolysis has not led to the widespread implementation of alteplase for acute ischaemic stroke in the United Kingdom. However, the Cochrane systematic review of thrombolysis for acute ischaemic stroke suggests that alteplase is the most promising treatment for acute ischaemic stroke. Successful implementation of thrombolysis in the United Kingdom will depend on continued investment in acute stroke services, attention to the known barriers to treatment, further data from randomized controlled trials and the licensing of alteplase for this indication.

Keywords: cerebrovascular disorders, thrombolytic therapy, random allocation

Introduction

It is now six years since the National Institute of Neurological Disorders and Stroke (NINDS) trial showed that alteplase (a recombinant tissue plasminogen activator) increased independent survival for highly selected patients with ischaemic stroke [1]. In this paper I will discuss why there has been a failure to implement treatment in the UK.

The excitement

The NINDS trial was unusually small (only 624 patients) but achieved a statistically significant result due to a major treatment effect (equivalent of 120 more independent survivors per 1,000 treated) [1]. The use of block randomization ensured that 302 of the 624 patients were recruited within 90 minutes. These results led to a licence for alteplase in the USA and Canada (and a restricted licence in Germany) for patients who could be assessed, scanned and treated within 3 hours of stroke onset.

The disappointment

The streptokinase trials were all stopped prematurely due to adverse events [2–4]. The subsequent alteplase trials were disappointing and possible reasons include: the play of chance; the use of heparin in the ECASS trials [5, 6]; a 6 hour time window; CT scan exclusion criteria in the ECASS trials and the larger dose of alteplase used in the first ECASS trial [5]. Despite the major endorsement of early alteplase treatment by many influential stroke neurologists, treatment had not been widely implemented by 1998 [7].

The reality

The mismatch between expert opinion and real life has become more obvious with time. In the USA, major centres are failing to treat more than 20% of the alteplase eligible patients [8] and there is virtually no routine use of alteplase in district hospitals in the UK or similar hospitals elsewhere. Audits have been conflicting: the STARS study suggested treatment could be successfully generalized (despite a third of patients treated outside the approved protocol) [9]; but the Cleveland study questioned the generalizability of alteplase [10].

The systematic review data suggests that alteplase is the most promising treatment for acute ischaemic stroke

A systematic review of thrombolysis is available in the Cochrane Library, and this type of review provides the least biased assessment of treatment effects. Some trial results may, by the play of chance, produce over-optimistic
estimates of treatment effects, other trials may produce pessimistic estimates. Overall, if treatment is effective, then the overall treatment estimate in a meta-analysis provides the least biased estimate of treatment effects [11]. This is relevant for thrombolysis as there is now some evidence that baseline imbalance contributed to the optimism of the most positive trial – the NINDS study [1, 12]. There is also evidence that the over-estimation of the NINDS study has been influenced by many factors [13, 14].

The updated Cochrane review includes data from 17 trials (5,210 patients) with the alteplase trials contributing about half the data in the overview. Eight trials evaluated intravenous alteplase (2,955 patients). In these studies, treatment was generally started within 3–6 hours of stroke onset and the benefits were substantial, with 57% dead or dependent in the control group compared to 51% in the alteplase group. This represents an additional 55 independent survivors for every 1,000 patients treated (95% CI 19–91). Overall, treatment with alteplase was associated with an excess of early fatal intracranial haemorrhage (ICH), from 1.0% in controls to 4.3% in treated patients, representing an additional 33 fatal ICHs for every 1,000 patients treated (95% CI 22–45). Data on symptomatic ICH showed an increase from 3% in controls to 10% in treated patients, representing an additional 70 symptomatic ICHs for every 1,000 patients treated (95% CI 53–88). A small excess of early deaths (7.1% vs 8.6%) was still apparent at the end of follow-up (13% vs 15%) representing an extra 19 deaths for every 1,000 patients treated (95% CI 6 fewer to 43 more).

These data suggest that, despite the risks of intracranial haemorrhage, alteplase is very effective for some highly selected patients, and the most promising treatment for a wider range of patients with acute ischaemic stroke. As ‘time is brain’, the benefits of alteplase are likely to be greater the earlier treatment is given and thus there is an expectation that 0–3 hour treatment will have a greater proportional benefit than treatment given later (e.g. 3–6 hours). In public health terms, more people are likely to be eligible for treatment 3–6 hours after stroke onset and generating more data for this subgroup of patients must be a priority.

When should you implement a thrombolysis service for ischaemic stroke?

In 1999 only half of all UK patients with stroke had access to a stroke unit [15]. The National Service Framework for Older People standard is that every general hospital should have a stroke unit by 2004 [16]. Stroke unit care is applicable to all patients with stroke and will, if adequately resourced, lead to about 50–60 extra survivors per 1,000 treated [17]. If your hospital does not have a stroke unit, this must be your priority. The public health benefit of organized stroke care is far more important than the projected benefit of early thrombolysis for stroke.

How do you implement a thrombolysis service?

When your hospital has an organized stroke service, you should then consider developing a thrombolysis service. There are currently two approaches being taken in the UK:

i. Implementation of the American Heart Association Protocol [18]

By late 2002, there is likely to be a European licence for alteplase for acute ischaemic stroke. It is likely that the license will have similar restrictions to the restricted licence granted in Germany i.e. an age limit of perhaps 75 to 80 years old (thus excluding about a third to half of all those with acute stroke) or anyone currently on an antiplatelet drug (about a third of all patients with acute stroke).

ii. Implementation of treatment based on the Third International Stroke Trial

Other centres have chosen to implement thrombolysis based around a double-blind, placebo controlled trial, the Third International Stroke Trial.

The Third International Stroke Trial (IST-3)

The protocol of the IST-3 has been published on the internet (available at http://www.dcn.ed.ac.uk/ist3). The treatment regime is based on the NINDS trial but with a time window extending up to 6 hours from stroke. The main phase of the IST-3 eventually plans to recruit up to 6,000 patients to provide sufficient statistical power to identify for whom treatment is particularly beneficial (or risky). The trial will examine the interaction between stroke subtype, age, stroke severity, CT scan appearances and delay to treatment. The planned expansion phase of the trial will help support expert centres develop appropriate thrombolysis protocols.

Early experience from the Stroke Association Start-up phase of the IST-3 has identified common barriers and some solutions (Table 1). Contrary to perceived opinion, many patients with stroke present to hospital early, with perhaps 50% arriving within 6 hours of symptom onset and removing hospital delays should be an early priority.

Summary

The National Service Framework for Older People has provided a clear mandate to improve acute stroke care and this will facilitate the development of a thrombolysis service for patients with acute ischaemic stroke.
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Table 1. Developing a stroke thrombolysis service: common barriers and suggested solutions

<table>
<thead>
<tr>
<th>Barrier to early thrombolysis for stroke</th>
<th>Solutions</th>
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</thead>
<tbody>
<tr>
<td>Failure to recognize stroke symptoms</td>
<td>Public education</td>
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<tr>
<td>Delays in admission to hospital</td>
<td>Ambulance protocols to “fast-track” patients</td>
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<tr>
<td>Delays in hospital emergency room</td>
<td>(e.g. those presenting within 5 hours of stroke onset)</td>
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<tr>
<td>Accurate stroke diagnosis</td>
<td>Appropriate nurse-led triage to acute stroke team</td>
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<tr>
<td>Difficulty getting urgent CT brain scan</td>
<td>Trained and available acute stroke team including senior staff (Specialist Registrars and Consultants)</td>
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<tr>
<td>Disorganized acute stroke admission system</td>
<td>Written, multi-disciplinary protocol (e.g. Integrated Care Pathway or Stroke Pathway)</td>
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<tr>
<td>Lack of knowledge</td>
<td>Training and education for stroke nurses and doctors</td>
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The table illustrates the common barriers and suggested solutions to the implementation of a stroke thrombolysis service.

Key points

- Thrombolysis, a promising treatment for acute ischaemic stroke, is rarely used in the UK.
- The uncertainty of the balance of risks and benefits of thrombolysis suggest that more trials are needed before thrombolysis is accepted in the UK.
- Substantial investment in stroke services, as envisaged in the National Service Framework for Older People, will be necessary to deliver thrombolysis safely in the UK.

Conflict of interest

Dr Lindley was editor of Stroke Matters (1997–2002) - a national stroke newsletter sponsored by Boehringer Ingelheim, the licence holders of alteplase, and as editor, has received sponsorship to attend international stroke conferences from the company.

References