Neurologists are generally steeped in the time-honoured tradition of making meticulous observations about individual patients. Our occasionally obsessive tendencies allow us to fixate on the details of a patient's history before performing a sophisticated physical examination, and (hopefully) arriving at a correct anatomical and pathological diagnosis for the particular problem. Recent technological advances have honed these diagnostic tools to an even finer edge. However, until fairly recently, the intellectual thrill of the neuro-diagnostic 'chase' went unmatched by the satisfaction of delivering effective treatment, leading to the 'nice job but so what' criticism often levelled at our speciality. To add a note of personal misgiving, the area within neurology that interests me most is stroke. I have lost track of the number of times that I have been told by other smug specialists, with a note of pity in their voices, that, 'It's all over as soon as the stroke has happened.' Of course, in the not too distant past, a diagnosis of ischaemic stroke would have been viewed pessimistically by health care professionals, patients and families, because there were no proven curative therapies. Although a proper 'cure' for stroke remains elusive, several recent interventions have been proven to save lives and reduce disability, including organized care on a multidisciplinary stroke unit (Stroke Unit Trialists' Collaboration 2001), and aspirin therapy within the first 48 h of stroke onset (Chen et al. 2000). Increasingly, ischaemic stroke is being viewed as a medical emergency requiring urgent treatment (Hill & Hachinski 1998), with a resultant increase in the interest in stroke medicine, and research into newer and more effective treatments. These changes are both timely and important, as stroke remains a formidable global problem that is only going to worsen as our populations age.
THE NINDS ACUTE STROKE TRIAL

It is for this reason that, when asked to write about an article that has changed my practice, I immediately thought of the one study in the area of acute stroke that has caused the most international controversy and debate – the National Institute for Neurological Diseases and Stroke (NINDS) trial of tissue plasminogen activator (TPA) for acute stroke (NINDS rt-PA Study Group 1995). Despite ongoing uncertainties surrounding the use of TPA, this trial has in many ways been the impetus for changing the way that we care for people with strokes. Some neurologists are now getting out of their beds in the middle of the night to go and see patients – an activity that would have been almost unheard of a short decade ago.

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Thrombolysis is one of the most exciting treatment options yet evaluated for acute stroke, because this is the only known therapy with the potential to actually reverse the stroke process. The use of clot busting drugs has a relatively long and successful history in the treatment of coronary artery disease (FTT Collaborative Group 1994), but, despite some early trials in the 1950s, has only been extensively studied in stroke patients for the past 10 years or so (Wardlaw and Warlow 1992). Following some early unsuccessful thrombolysis trials in acute stroke, the NINDS trial was eventually published in 1995 (NINDS rt-PA Study Group 1995), and TPA received approval from the American Food and Drug Association soon afterwards (Anonymous 1996a), with several sets of guidelines subsequently published (Adams et al. 1996; National Stroke Association 1993; Pessin et al. 1997). Because it was the first randomised controlled clinical trial to provide evidence of benefit for an albeit highly selected group of people with acute stroke, the NINDS trial was received with tremendous enthusiasm in the United States, and enjoyed fairly extensive media coverage (Gorman 1996). The use of TPA even became part of the plot in an episode of ‘ER’, a popular American television programme (National Broadcasting Corporation 1997). In February 1999, the Therapeutic Products Directorate of Health Canada conditionally approved the use of TPA for acute stroke within three hours of symptom onset (Anonymous 1999a), a decision based primarily on the evidence provided by the American NINDS trial (NINDS rt-PA Study Group 1995). Canadian treatment guidelines were subsequently published (Norris et al. 1998), followed by the development of similar acute thrombolysis programmes in major Canadian centres (including my own), accompanied by national media coverage (Foss 1999; Evenson 1999; MacKinlay 1999).

BUT, A NOTE OF CAUTION

However, despite being heralded as a new standard of care by many, the increased use of TPA has not been universal, and this ‘chemical neurosurgery’ remains a highly controversial subject. The actual frequency with which TPA is being given for acute ischaemic stroke in the United States is quite low, with only about 1.5% of eligible patients described as actually receiving it in one published report (Alberts 1998), although other postmarketing surveillance studies suggest slightly higher rates of use, but with few reports consistently above 5%.

One reason for this rather poor showing may be the substantial variation in the attitudes of clinicians (neurologists, internal medicine specialists, geriatricians and emergency physicians) about the safety and applicability of TPA within and between different countries. Where I work in Canada, there are now two published sets of conflicting recommendations dealing with the use of TPA. Neither the Canadian Stroke Consortium (Norris et al. 1998) nor the American Heart Association (Adams et al. 1996) advocate the use of TPA for patients who meet criteria largely specified in the NINDS trial (NINDS rt-PA Study Group 1995). On the other hand, recent recommendations from the Canadian Association of Emergency Physicians (CAEP 2001) are generally more conservative. The CAEP
Guidelines recommend that stroke thrombolysis should be limited to centres with appropriate neurological and neuro-imaging resources that are capable of administering treatment within 3 hours. In such centres, emergency physicians should identify eligible patients, initiate low risk interventions and facilitate prompt computed tomography. Only physicians with demonstrated expertise in neuroradiology should interpret head CT scans used to determine whether to administer thrombolytic agents to stroke patients. Neurologists should be directly involved prior to the thrombolytic administration.

Other related problems include a lack of patient awareness of the symptoms and importance of stroke, and prehospital and hospital infrastructures that are presently at odds with the very short assessment and treatment window necessary for thrombolysis for stroke (Wester et al. 1999).

As well as inciting debate in the medical literature (Brott et al. 1996; Caplan et al. 1998; Horowitz 1998; Li 1998; Anonymous 1996b), several general reviews and consensus statements (Gibitz et al. 1999; Anonymous 1999b; Royal College of Physicians of Edinburgh 1999; Anonymous 1997) have since been published that argue against the routine use of TPA for persons with acute ischaemic stroke, and have called for randomised trials to further evaluate this therapy.

CONTINUING UNCERTAINTY

It cannot be denied that the results of the NINDS TPA trial (NINDS rt-PA Study Group 1995) have transformed how many clinicians think about the management of some people with acute stroke. For me, one of the most beneficial outcomes of the NINDS trial has been the controversy that has resulted from it, and the genuine lack of certainty that I feel when confronted with an otherwise perfectly eligible patient three and a half hours after their stroke has started. I suspect that many of my colleagues feel the same way (even if they won’t admit it!). Some patients I treat, but only within three hours, and only if I’m certain. The majority of patients go untreated; I simply don’t know what the correct action is, as many of my patients don’t fit the general profile of those enrolled in the published trials. The patients I see are often older, with other medical problems, and many will have early changes (subtle and otherwise) on their CT scans.

As I see it, uncertainty is a useful marker for the need for further understanding. If we are to make the best possible decisions about care for patients, it is important to systematically consider all of the available evidence rather than to rely on information from individual clinical trials. A systematic review of all the randomised evidence provides a more precise estimate of treatment-effect by reducing the effects of random error and systematic bias (Counsell et al. 1995). Such an approach may also explain inconsistencies between trials, and may generate new research questions. Uncertainty about the NINDS trial led me to seek further information about the complex and thorny issue of TPA in acute stroke by introducing me to a systematic review of all of the randomised trials of TPA in acute stroke (Wardlaw et al. 2001).

The systematic review, published and updated on a regular basis on the Cochrane Library, includes 17 unconfounded, truly randomised clinical trials with a total of 5144 patients comparing intravenous thrombolytic treatment with placebo in patients with acute ischaemic stroke of less than 6 h duration (Wardlaw et al. 2001). In all trials, a computed tomographic (CT) or magnetic resonance (MR) scan was performed before randomization to exclude intracranial haemorrhage or structural stroke mimics. The systematic review included information on three different thrombolytic agents: streptokinase, urokinase and TPA. Over 50% of the data (2889 patients, including the NINDS trial) compared TPA with control in acute ischaemic stroke.

In the systematic review (Wardlaw et al. 2001), the absolute risk of symptomatic intracranial haemorrhage was increased in the TPA-treated group, corresponding to 73 additional symptomatic haemorrhages. However, the number of patients dead or dependent at the end of the follow-up period (considered by many to be the most important outcome) was markedly reduced. The systematic review demonstrated that 57 additional patients (95% CI 55–90 additional haemorrhages). However, the number of patients dead or dependent at the end of the follow-up period (considered by many to be the most important outcome) was markedly reduced. The systematic review demonstrated that 57 additional patients (95% CI 20–93) were alive and independent at the end of follow-up for every 1000 patients treated with thrombolysis within six hours of stroke onset. By way of comparison, thrombolysis for acute myocardial infarction results in an absolute mortality reduction of 30 per 1000 if treatment is given within the first 6 h of symptom onset (FTT Collaborative Group 1994).

A subgroup analysis suggested that the balance of risk and benefit may be related to the
timing of TPA administration, with a more favourable outcome if TPA is given within three hours of onset. It should be recognized that this subgroup analysis was based on data from only 869 patients from three trials (Anonymous 1996a; Cochrane Stroke Review Group 1999; Hacke et al. 1995), with the NINDS trial (Anonymous 1996a) contributing over 50% of the information. In addition, the authors of the review speculated upon imbalances in the baseline variables that could have introduced other biases. Despite these limitations, the reduction in the number of patients dead or dependent at the end of follow-up was striking, which, if proven to be true, would be consistent with 140 additional patients alive and independent for every 1000 patients treated with TPA within three hours of stroke onset (95% CI 77–203 more patients with a good recovery; \(P = 0.00002\)).

It is worth noting that the number for the NINDS trial alone was 160 additional independent survivors; 95% CI 87–234. The systematic review (Wardlaw et al. 2001) demonstrated a trend for greater benefit if TPA was given earlier on, but no obvious cut off point at which TPA stops being effective was identified. There may be benefits beyond the three-hour time window. Unfortunately, the time at which the risk of TPA outweighs the benefits is not known; there is insufficient randomised evidence at present to state this with any certainty.

At face value, this is very striking. A treatment-effect of this magnitude has never before been seen in acute stroke. However, this result is largely due to a difference of only 50 fewer dead or dependent patients in the TPA treated group of the NINDS trial (the only ‘positive’ trial). The estimate of the treatment-effect, although statistically significant, is not very robust, and could be altered completely by comparatively small changes in the raw data. Estimates based on a small number of outcome events are more likely to be subject to bias (systematic error) and the play of chance (random error) than estimates based on a large number of outcome events. Indeed, further analysis of this three-hour data demonstrates a statistically significant difference (heterogeneity) between the results of the three trials implying that factors other than chance are at play. While it is possible to speculate on the potential cause(s) of this heterogeneity, the differences cannot be adequately explained by the existing data. Therefore, while the data cannot be disputed, it is reasonable to caution against over-emphasis of the results of one very positive trial.

**THE NEED FOR MORE RANDOMISED TRIALS**

It has been demonstrated that TPA given to (highly selected) patients in specialist centres within three hours of acute ischaemic stroke onset reduces the overall risk of death and dependency in the long term, but this benefit may be offset somewhat by an increased short-term risk of intracranial haemorrhage. Despite the recent licensing of TPA and the development of treatment guidelines in North America, the balance between the risks and benefits from thrombolysis in acute ischaemic stroke remains in many ways unclear. It is still not clear exactly which stroke patients stand to benefit from or be harmed by TPA. More data are needed to clarify the time window during which TPA can be safely administered, the role of initial stroke severity, the significance of early visible ischaemic changes on CT scan, the use of TPA in older patients, the generalisability of thrombolysis in less experienced centres and the cost-effectiveness of TPA.

The answers to the questions posed in the systematic review will only be found in further research. One solution to the uncertainty created by the NINDS trial is a new randomised trial sufficiently powered to deal with the unresolved questions. Our stroke group in Halifax is becoming involved in just such a trial. The Third International Stroke Trial (IST-3) is an international, multicentre, randomised, double-blind, placebo-controlled trial of TPA in acute stroke presenting up to six hours after symptom onset. The trial is presently in the pilot phase, and is recruiting interested centres for the main phase of the trial. The IST-3 plans to randomise at least 6000 patients from both urban and rural centres. Further information about the IST-3 may be obtained from the IST-3 website: http://www.dcn.ed.ac.uk/ist3.

**REFERENCES**


