A PAPER THAT CHANGED MY PRACTICE

Curiously, the paper that changed Geoff Donnan's practice is the very same one that changed Gord Gubitz's practice (Gubitz 2002). Maybe this is because both subspecialize in stroke, and because for stroke doctors to come rushing into hospital to give a treatment that might actually work has come as something of a culture shock.

Charles Warlow, Editor

The NINDS trial of thrombolysis in acute ischemic stroke

Geoffrey A. Donnan

National Stroke Research Institute, Gate 10, Banksia Street, Heidelberg West Victoria, Australia;
E-mail: donnan@austin.unimelb.edu.au
Practical Neurology, 2002, **3**, 178–81

A paper that changed my practice: which tug-boat turned the Queen Mary? My immediate thoughts revolve around such issues as the nature of my practice and any really dramatic changes that have occurred over the nearly 20 years since I became a neurologist. If they have occurred, were they in clinical assessment and diagnostic approaches, general management or treatment? Mmm.

To lay my cards on the table: I am an academic neurologist who sees patients every day as inpatients or outpatients, mainly those with an acute stroke, but also patients with general neurological problems. Upon reflection, there is not much doubt that the most dramatic change in my practice pertains to the former group, those who have had an acute stroke. When I first became interested in this aspect of neurology, what mainly appealed was the myriad of clinical presentations and subtypes of stroke and the clinical challenge of determining the most likely mechanism of the event and its probable outcome. At the same time, there was an inherent frustration because of the lack of any opportunity to intervene in a therapeutic sense. To watch a person with an acute hemispheric syndrome due to an embolus lodged at the mid-

dle cerebral artery origin and to know that by simple removal of the clot, complete recovery could occur was frustrating. We already knew that spontaneous recanalization did often occur due to endogenous thrombolysis and haemodynamic factors. Sometimes the embolus was seen angiographically or by ultrasound techniques: so near and yet so far. Then came thrombolysis.

Thrombolysis had been emerging slowly over a number of years. There had been anecdotal series published in which a variety of thrombolytic agents administered by differing routes were described. There were a few randomized controlled trials but these were small or depended on surrogate endpoints for clinical outcomes such as arterial recanalization rates.

Studies such as these had become feasible because of the introduction of computerized tomography (CT) in the 1970s. This imaging modality was well suited to acute stroke assessment because an almost instantaneous distinction could be made between intracerebral haemorrhage and infarction. Haemorrhage appeared as a white blob that could even be recognized by technologically-challenged neurologists after fairly brief training periods. Although the topography of infarction could not be ascertained for about 12 h post-stroke with any certainty, this problem was soon overcome by magnetic resonance imaging techniques, which appeared about a decade later. Diffusion- and perfusion-weighted images are now used to give topographical detail of early patterns of infarction and perfusion defects, although MRI

within the hierarchy of
evidence the highest level
demands an overview
analysis of all the available
evidence: hence to
discuss a single paper
that changes practice is a
contradiction in terms for
evidence-based medicine
adherents

is a more limited resource in most countries and CT remains the workhorse of acute stroke imaging (Hand & Wardlaw 2001).

While these imaging developments had allowed investigators to seriously consider thrombolysis as a potential means of recanalising occluded arteries, there was still the very real concern about intracerebral haemorrhage as a consequence of the thrombolytic process. It was already known that this could be a naturally-occurring phenomenon after recanalization, if this occurred late enough for blood–brain barrier integrity to be compromised. The proportion of cases in which this was likely to occur was uncertain and estimates ranged from about 3–15%, depending on the definition of haemorrhage and the time the identifying image (CT) was performed. Whatever the thrombolytic agent used or route of administration, it was realized that a balance of risks and benefits for this form of therapy would need to be entertained. By the early 1990s, this balance was being put to the test in a number of well-conducted randomized controlled trials using streptokinase and tissue plasminogen activator (tPA).

The first major randomized controlled trial to show a positive benefit for any thrombolytic agent in terms of improved clinical outcomes was conducted by the National Institute of Neurological Disorders and Stroke (NINDS) study group: this is the paper that has been one of the most significant in changing my clinical practice (The NINDS rt-PA Study Group 1995). It could not be said that this change in practice occurred immediately, as will become clear. Nor could it be said that acceptance of evidence from this paper has been uniform world-wide. Why is this so?

First, to the paper itself. The investigators showed that for patients with any form of ischaemic stroke (large artery, cardioembolic, small artery or posterior circulation) the administration of 0.9 mg/kg of tPA intravenously within 3 h of symptom onset improved outcomes at 3 months by about 30%, i.e. the proportion of patients who had recovered to the point that they had little or no residual neurological defect and could, in essence, walk home. The study conduct was excellent with a double blind randomized controlled design and a sample size of 624. Almost half the patients were randomized within 90 min of stroke onset, a remarkable achievement considering the barriers to rapid recognition of symptoms, transportation and timely management in emergency departments of patients with stroke. Importantly, there appeared to be no increase in mortality associated with therapy, although there was about a 7% symptomatic intracerebral haemorrhage rate (i.e. worsening neurological deficit in the presence of a haemorrhage). Hence, the original thoughts about having to balance risks and benefits for thrombolytic therapy were correct: the problem being that the patients who were most likely to benefit and those at risk of haematoma formation were not particularly evident.

But surely this one paper was not enough evidence to change my practice completely? We all know that within the hierarchy of evidence the highest level demands an overview analysis of *all* the available evidence: hence to discuss a single paper that changes practice is a contradiction in terms for evidence-based medicine adherents, as most of us are. Indeed, a number of independent

trials were conducted: three using streptokinase as the thrombolytic agent within 4 or 6 h post-stroke, all of which increased mortality and did not improve outcomes. Three others in which tPA was used with a 6 h time window and doses of 1.1 mg/kg and 0.9 mg/kg showed trends toward better outcomes. When an overview analysis of all the data available where intravenous tPA is used within 3 h of stroke onset is considered, a clear benefit is seen with a relative risk reduction of about 44% for death and disability combined, an absolute reduction of about 13%, so that the number of people needed to treat to prevent one becoming dead or disabled is about eight, powerful medicine in anyone's language. The evidence from the NINDS trial alone was enough to convince the Federal Drug Administration (FDA) that tPA should be licensed in the United States. Canada, a number of European and South American countries have followed suit, but the move has been far from universal. For example, tPA is not licensed for use in the UK, Australia or New Zealand. So how has all this altered my practice and how?

To me, the evidence that tPA is effective when given intravenously within 3 h of ischaemic stroke onset is adequate. At our centre, and a number of similar centres in Australia, tPA is now given routinely to patients fulfilling the NINDS protocol criteria. To return to my starting point, here is the first major shift in how I manage patients with acute ischaemic stroke: contrary to my original vision of practice during my time, I am now offering a routine form of acute therapy to stroke patients. This has had a considerable impact on the organization of stroke services. Although we have had a stroke unit in operation since 1977, it was geographically dispersed. This structure did not lend itself to a consistent acute stroke management strategy, particularly for protocol-driven therapies such as tPA. Hence, a reorganization of our existing resources occurred so that all patients with stroke were admitted to a high dependency area where neurological and haemodynamic monitoring could take place during the first 48 h. Once stable, the patients were transferred to a less intensely-monitored area and active rehabilitation started.

While many neurologists and stroke physicians accept that there is enough evidence to be convinced that tPA should be given routinely within 3 h of ischaemic stroke onset, this view is by no means universal. The reasons include

To me, the evidence that
tPA is effective when
given intravenously within
3 h of ischaemic stroke
onset is adequate

the perceived need to replicate the NINDS trial rather than depend on the meta analysis that includes this single trial plus smaller amounts of data from longer time-window studies. Furthermore, there are areas of uncertainty that require clarification, such as should those with very severe clinical deficits, the elderly, or those with significant early ischaemic changes on CT receive tPA? For this reason, the newly-initiated trial (International Stroke Trial-3) where patients will be randomized up to 6 h after stroke onset, is reasonable. Clinicians who feel that enough data are available within 3 h, can still randomize patients at 3–6 h, while those who feel greater uncertainty can enter patients within the full 6 h range the trial allows.

So, the thrombolysis story is at an interesting point of evolution. A paper has been pivotal in changing my practice to routine administration of tPA within 3 h of ischaemic stroke onset, but many other factors have contributed. Interestingly, this approach is not universal: the uncertainty principal is alive and well!

REFERENCES

- Gubitz G (2001) The NINDS trial of thrombolysis in acute ischaemic stroke. *Practical Neurology* 2, 45–49.
- Hand PJ & Wardlaw JM (2001) CT for acute ischaemic stroke. *Practical Neurology* 1, 82–92.
- The National Institute of Neurological Disorders and Stroke rt-PA Study Group (1995) Tissue Plasminogen activator for acute ischemic stroke. *New England Journal of Medicine*, 333, 1581–7.