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Tissue plasminogen activator for acute ischaemic stroke

A recent study of a thrombolysis protocol for patients with acute stroke, and an accompanying editorial, prompted debate about the safety and efficacy of tissue plasminogen activator in stroke, and the data supporting its use for this indication. (MJA 2007; 187: 567-570 and 548-549)

James C Hurley

TO THE EDITOR: The recent report on the use of a stroke thrombolysis protocol by Batmanian and colleagues¹ raises many issues. The most recent guidelines regarding thrombolytic therapy for ischaemic stroke recommend that "If thrombolytic therapy is to be used . . . consultation with a neurologist or stroke physician is essential before instigating therapy. Strict adherence to the inclusion and exclusion criteria is important . . ."² Hence, I find the integral role of a neurologist in Batmanian and colleagues' protocol reassuring.

However, consent to therapy in this setting is not simple. In the protocol, they informed the patient and/or next of kin about the risks and benefits of thrombolysis, but did they seek informed consent? The benefits of thrombolytic therapy are controversial, and equipoise exists.

Reflecting this, a multicentre trial³ is underway that includes patients who meet the eligibility criteria of Batmanian et al's protocol. The evidence cited by Batmanian and colleagues in support of thrombolysis was based on small randomised trials published more than a decade ago.⁴ Further, the summary results of the meta-analysis they cited are associated with significant heterogeneity and lose statistical significance with the inclusion of additional results from observational studies⁵ (Box).

Moreover, the more recently published audits and the analysis that led to the number-needed-to-treat estimate cited by Batmanian et al were based on comparisons with a reference group dominated by the placebo group of the NINDS (National Institute of Neurological Disorders and Stroke) trial.⁶ This trial has been criticised for likely faulty randomisation resulting in baseline disparities unfavourable to the placebo

recipients. These projections of benefit based on comparisons with a small and non-representative placebo group from a trial published over a decade ago are misleading. A calculation of numbers needed to treat based on such limited evidence, particularly for a soft endpoint such as assessment of disability, is hazardous and potentially misleading.⁷

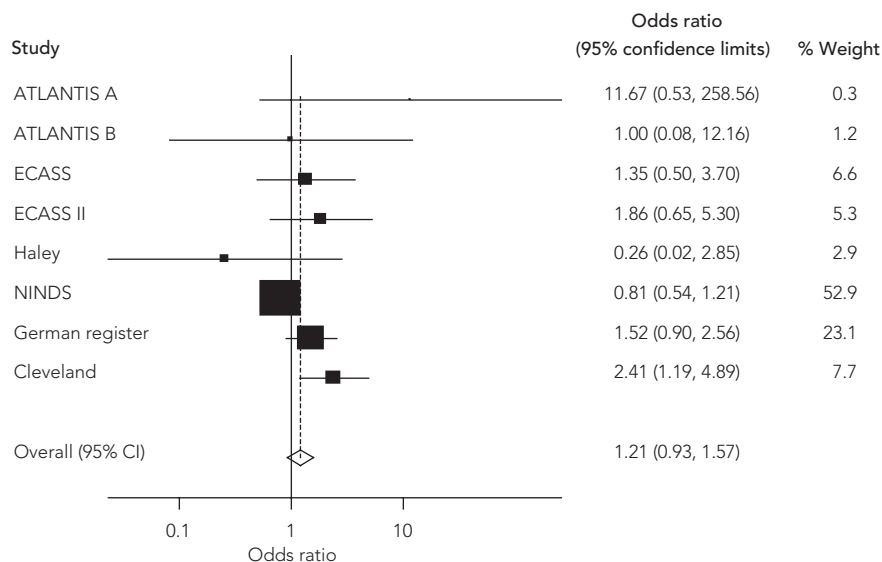
There are other important issues associated with this therapy that need to be resolved. For example: Are mortality rates increased in groups receiving tissue plasminogen activator therapy in non-teaching hospitals?⁸ Is this therapy safe in older people?; and finally, does this therapy not have the proven mortality risk associated with streptokinase in randomised trials in patients with stroke?⁴

Thrombolysis for stroke requires more evidence from randomised trials, not more protocols. Trials including older people are especially needed, given the age-dependent mortality risk associated with this therapy.

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- 1 Batmanian JJ, Lam M, Matthews C, et al. A protocol-driven model for the rapid initiation of stroke thrombolysis in the emergency department. *Med J Aust* 2007; 187: 567-570.
- 2 Neurology Expert Group. Therapeutic guidelines: neurology, version 3. Melbourne: Therapeutic Guidelines Limited, 2007.
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- 4 Wardlaw JM, del Zoppo G, Yamaguchi T, Berge E. Thrombolysis for acute ischaemic stroke. *Cochrane Database Syst Rev* 2003; (3): CD000213.
- 5 Hurley JC. Hazards of thrombolytic therapy for stroke: the real-world experience [letter]. *Intern Med J* 2007; 37: 348-349.
- 6 Tissue plasminogen activator for acute ischemic stroke. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. *N Engl J Med* 1995; 333: 1581-1587.
- 7 Koziol JA, Feng AC. On the analysis and interpretation of outcome measures in stroke clinical trials: lessons from the SAINT I study of NXY-059 for acute ischemic stroke. *Stroke* 2006; 37: 2644-2647.
- 8 Reed SD, Cramer SC, Blough DK, et al. Treatment with tissue plasminogen activator and inpatient mortality rates for patients with ischemic stroke treated in community hospitals. *Stroke* 2001; 32: 1832-1840. □

Odds ratios for fatal outcome from published cohorts of patients receiving tissue plasminogen activator therapy within 3 hours of onset of acute ischaemic stroke



The addition of two recent observational cohorts, the German Stroke Register and the Cleveland experience, to the meta-analysis of six controlled trials as reported in Wardlaw et al⁴ increases the summary odds ratio from 0.97 (95% CI, 0.69–1.36) to 1.21 (95% CI, 0.93–1.57). (Figure reproduced from Hurley⁵ with permission from Wiley-Blackwell Publishing Ltd.)

ATLANTIS = Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke.
ECASS = European–Australasian Cooperative Acute Stroke Study.
NINDS = National Institute of Neurological Disorders and Stroke. ♦

Gino J Toncich

TO THE EDITOR: The assertion of Davis and Batmanian and their colleagues that thrombolytic treatment for ischaemic stroke is reasonably safe and highly effective^{1,2} is not supported by the primary randomised trials of its use.³

Is tissue plasminogen activator (tPA) safe? It remains undisputed that none of the trials for thrombolysis in stroke have shown any mortality benefit.⁴ All of the trials have shown increases in symptomatic intracranial haemorrhage; in the NINDS trial, the increase was from 0.6% in the placebo arms to 6.4% in the treatment arms — a 1000% relative increase — and 45% of those with symptomatic bleeds died.⁵ Presumably, any mortality benefit from opening blocked arteries is lost because of the increased mortality from intracranial bleeding. Therefore, the drug is not safe.

Is tPA effective? Thrombolysis for acute myocardial infarction was assessed in tens of thousands of patients in many independent studies, with virtually all showing clear mortality benefit. By comparison, the stroke thrombolysis literature is full of negative studies, with only one positive result. The NINDS trial⁴ stands alone as the only randomised controlled trial (RCT) providing positive evidence for thrombolysis for stroke. Ignoring criticisms of its interpretations and methodology, of which there are many, it had fewer than 600 patients and its results have not been reproduced independently.

Breaches of protocol continue to be published. Batmanian and colleagues gave patients tPA after 180 minutes despite all the evidence saying this has no benefit, justifying it by saying the decision had been made at 170 minutes.²

Davis and colleagues¹ based their claims of safety and efficacy on registries, subgroup analyses, meta-analyses, and expert panels all based on the same single RCT — the NINDS trial.⁴ This is low-grade evidence for a potentially lethal therapy.

It is time a major RCT was done to repeat the NINDS trial and finally determine whether its result was a statistical anomaly or a real effect. There is no shortage of stroke patients — Batmanian et al found that 14% of patients were eligible for this therapy.²

The paucity of evidence for thrombolysis for stroke does not justify rushing patients to stroke centres, bypassing perfectly good hospitals in the hope of finding some of the 3% of patients eligible for treatment, of

whom one in eight (0.38% of all stroke patients) would theoretically have a better neurological symptom score if given thrombolysis.^{6,7} I feel that it is a waste of time and effort, and a danger to patients, to focus all resources on supplying a potentially lethal therapy that is often incorrectly used and provides a marginal benefit.

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- 1 Davis SM, Hand PJ, Donnan GA. Tissue plasminogen activator for ischaemic stroke: highly effective, reasonably safe and grossly underused [editorial]. *Med J Aust* 2007; 187: 548-549.
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- 3 Hoffman JR. Tissue plasminogen activator (tPA) for acute ischaemic stroke: why so much has been made of so little [editorial]. *Med J Aust* 2003; 179: 333-334.
- 4 Hacke W, Donnan G, Fieschi C, et al. Association of outcome with early stroke treatment: pooled analysis of ATLANTIS, ECASS and NINDS rt-PA stroke trials. *Lancet* 2004; 363: 768-774.
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Daniel M Fatovich

TO THE EDITOR: I found it ironic to read the recent editorial by Davis and colleagues endorsing the use of tissue plasminogen activator (tPA) therapy for stroke patients.¹ The irony relates to the fact that a week later I attended the annual scientific meeting of the Australasian College for Emergency Medicine, where data were presented (Hoffman J. New information on the use of tPA in acute ischaemic stroke. 24th Annual Scientific Meeting of the Australasian College for Emergency Medicine; 2007 Nov 25–30; Gold Coast, Qld) that cast strong doubt on the conclusions derived from the NINDS trial.²

There are further objections to the claim that the value of tPA has been adequately proven,³ none of which are remotely addressed by the editorial.

As an emergency physician, this dichotomy of opinion is frustrating. There is obviously conflicting evidence, which usually

means that data are insufficient. Hence, until more research is completed, especially clinical trials that replicate the original NINDS study, the claim of Davis et al that tPA is “highly effective, reasonably safe and grossly underused”¹ is inappropriate.

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- 1 Davis SM, Hand PJ, Donnan GA. Tissue plasminogen activator for ischaemic stroke: highly effective, reasonably safe and grossly underused [editorial]. *Med J Aust* 2007; 187: 548-549.
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- 3 American Academy of Emergency Medicine. Position statement on the use of intravenous thrombolytic therapy in the treatment of stroke. Milwaukee, Wis: AAEM, 2002. <http://www.aaem.org/position-statements/thrombolytictherapy.php> (accessed Feb 2008).

Julia J Batmanian, Meeyin Lam, Caitlin Matthews, Andrew Finckh, Martin Duffy, Robert Wright, Bruce J Brew and Romesh Markus

IN REPLY: We welcome the opportunity to respond to issues raised by Hurley and Toncich. Australian, United States and European stroke guidelines based on level 1, grade A evidence recommend intravenous recombinant tissue plasminogen activator (IV-rtPA) for patients with acute ischaemic stroke (AIS) who meet specific inclusion criteria and present within 3 hours of AIS onset.^{1,2} Recombinant tPA is approved for this indication by the Therapeutic Goods Administration.

We obtained informed consent before thrombolysis, but recognise that this is challenging because of the urgent need to initiate treatment, rather than doubts regarding benefit.

A Cochrane systematic review of eight randomised controlled trials (RCTs), which together comprised 2955 patients, concluded that IV-rtPA within 3 hours of AIS onset was more effective in reducing death or dependency (odds ratio [OR], 0.66; 95% CI, 0.53–0.83), with no statistically significant adverse effect on death (OR, 1.13; 95% CI, 0.86–1.48).³ The Third International Stroke Trial (IST-3), which Hurley cites to support his view that sub-3-hour stroke thrombolysis remains controversial, was in fact designed to address *different* issues: effi-

cacy of rtPA given 3–6 hours after symptom onset and to those aged over 80 years, as well as imaging predictors of response.

We believe Hurley's figure from his own letter is an incorrect attempt at meta-analysis. He combines data from RCTs and selected observational studies (excluding the Safe Implementation of Thrombolysis in Stroke Monitoring Study [SITS-MOST] of 6483 patients⁴), a method subject to selection bias.

Although the original Cleveland study (as cited by Hurley) showed high rates of intracranial haemorrhage, 50% of patients in the study were not treated according to the protocol. The incidence of intracranial haemorrhage was subsequently reduced to the expected level following implementation of a quality improvement program to ensure strict adherence to protocols.⁵ Hurley suggests that projections of IV-rtPA benefits are misleading because of baseline imbalances in the NINDS trial. These concerns were addressed by reanalysis of the data by an independent committee commissioned by NINDS,⁶ which not only reconfirmed the original results but suggested an even greater benefit for AIS patients receiving IV-rtPA.

We believe Hurley's statement that mortality rates are increased when stroke thrombolysis occurs in non-teaching hospitals is unsubstantiated. In the study cited, mortality rates were similar to those observed in RCTs of IV-rtPA, with no difference between teaching and non-teaching hospitals.⁷ Indeed, large registries in Europe (where 50% of centres had little or no prior experience)⁴ and in Canada⁸ report efficacy rates following thrombolysis similar to those from RCTs with lower rates of intracranial haemorrhage and mortality.

In our view, IV-rtPA within 3 hours of AIS does not require more RCT evidence. Due to therapeutic inertia, only a small proportion of eligible stroke patients receive this therapy. Comprehensive acute stroke protocols in the emergency department in partnership with stroke clinicians could improve delivery of this highly effective treatment.

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Stephen M Davis, Peter J Hand and Geoffrey A Donnan

IN REPLY: Stroke experts around the world consider that the evidence for thrombolysis with tissue plasminogen activator (tPA) within 3 hours is overwhelming. Licensing authorities such as the Therapeutic Goods Administration in Australia and the Food and Drug Administration in the United States have approved use of tPA after rigorous, independent analysis of all the available data. However, it seems that a minority of sceptical emergency physicians remains, who will probably never be convinced. Further trials in the sub-3-hour time window are unlikely to receive ethical approval. The focus of stroke research has now moved on. Current targets include expansion of the time window and alternative approaches to recanalisation such as intra-arterial thrombolysis and clot retrieval.

Hurley states that there was a baseline imbalance in the pivotal NINDS trial in favour of tPA. We think this old chestnut was laid to rest by an independent reanalysis of the NINDS data.¹ The quoted Cochrane

review included all thrombolytic agents (such as the now-abandoned streptokinase),² whereas meta-analyses restricted to tPA alone are unequivocally positive.³ The figure presented by Hurley is misleading, combining both randomised controlled trials and selected population registries — yet excluding SITS-MOST, an observational study of 6483 patients.⁴

Both Toncich and Fatovich criticise the trial evidence. This contrasts not only with the virtually universal expert opinion of stroke clinicians, but also with the opinion of many emergency physicians.^{5,6} Indeed, the INSTINCT (Increasing Stroke Treatment through Interactive behavioral Change Tactics) trial aims to identify local barriers to the use of tPA in emergency departments, with the goal to increase appropriate use of tPA in acute ischaemic stroke.⁵

Finally, stroke physicians do not need to be neurologists. We consider that most general physicians, and indeed emergency physicians, should acquire the core skills to deliver intravenous tPA in acute ischaemic stroke. Would anyone familiar with modern stroke medicine deny tPA to an otherwise well 65-year-old with hemiparesis who presents 90 minutes after symptom onset? It is critical that all eligible patients in Australia are offered this licensed therapy.¹⁻⁶

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