

# Tissue plasminogen activator for ischaemic stroke: highly effective, reasonably safe and grossly underused

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*Australian health systems must rise to the challenge of providing thrombolysis to more stroke patients*

The substantial benefits and relative safety of tissue plasminogen activator (tPA) for acute ischaemic stroke within 3 hours of symptom onset have been accepted by stroke clinicians around the world.<sup>1</sup> It is one of the most effective treatments in acute medicine, with a 30% increase in excellent outcomes and a “number needed to treat” for clinical improvement as low as three patients.<sup>2</sup> A European register of 6483 patients (SITS-MOST, Safe Implementation of Thrombolysis in Stroke Monitoring Study) indicated that tPA is safe and effective, even when used in relatively inexperienced centres.<sup>3</sup> The clinical benefits overwhelm a small rate of bleeding complications, chiefly symptomatic haemorrhagic transformation of the infarct. The rate of symptomatic intracerebral haemorrhage was actually lower in this large register than in the earlier randomised clinical trials.<sup>3</sup> Small Australian tPA audits have confirmed these conclusions.<sup>4,5</sup> Based on level 1 evidence, the therapy was licensed in Australia in 2003, and is recommended in Australian, North American and European stroke guidelines.<sup>6</sup> However, despite this overwhelming information, probably some thousands of Australian patients are effectively denied tPA each year.<sup>7</sup> This is a major challenge for our health system.

Batmanian and her colleagues have made an important contribution (*page 567*),<sup>8</sup> demonstrating that a 24-hour comprehensive protocol delivered by a team involving emergency physicians and stroke neurologists can deliver thrombolysis to 14% of their acute stroke patients. This figure is in line with the best international stroke centres. The involvement of emergency physicians is essential to optimise the delivery of tPA, particularly given the worldwide shortage of stroke specialists. With a protocol aimed at rapid triage, assessment and investigation of stroke patients, Batmanian et al have shown that nearly all eligible patients can receive thrombolytic therapy. Their centre at St Vincent's Hospital (Sydney) and other Australian centres are participating in the ongoing SITS international registry, aimed at auditing the efficacy and safety of tPA for acute stroke. Nearly 400 Australian patients have now been entered on this registry, with safety of tPA consistent with the benchmark European figures (Dr M Parsons, neurologist, John Hunter Hospital, Newcastle, personal communication).

A key barrier to the use of tPA is delayed arrival to hospital after stroke onset. In the St Vincent's study, 40% of patients arrived within 3 hours, a higher rate than in many centres. Improved access to tPA and other acute stroke therapies can be enhanced by public education about stroke symptoms (such as the *FAST: Face, Arm, Speech, Time* campaign of the National Stroke Foundation in Australia), followed by rapid ambulance transport to a hospital with an organised acute stroke team. The public must be educated to call an ambulance, not a general practitioner, when stroke symptoms occur. Australian studies have confirmed that ambulance officers can accurately diagnose most strokes.<sup>9</sup> Ideally,

paramedics inform the emergency department of their impending arrival, facilitating the 60-minute “door to needle” target time for tPA therapy.

Implicit in achieving good outcomes after therapy is rapid access to a stroke care unit (SCU), the benchmark for optimising outcomes in a condition with a high mortality rate and the commonest cause of disability in our society.<sup>10</sup> Stroke strategies in most Australian states have been developed to increase the access of acute stroke patients to SCUs, which are expert multidisciplinary and geographically localised units, using evidence-based protocols for acute stroke therapy. In Australia, these are generally not intensive care units (ICUs), although cardiac monitoring is desirable during the acute period. In the St Vincent's study, patients were monitored in the ICU for up to 24 hours, because the protocol mandated a 1:2 nursing care ratio. We generally admit tPA patients to our SCU during or after the initial 1-hour infusion in the emergency department. Our SCUs use a 1:4 nursing ratio. We do not consider that ICU management is needed for most patients, but acknowledge that differing models will suit different institutions.

Acute reperfusion therapy is the most promising approach for acute stroke. The evidence for efficacy of tPA within 3 hours is overwhelming, although there is still some debate about treatment in the very elderly, patients with very severe neurological impairment, or those with extensive early ischaemic changes on computed tomography (CT) scan.

Meta-analysis of the tPA trials shows that there are treatment responders beyond 3 hours. A number of trials, such as the ECASS 3 and the IST 3 trials, are aimed at extending the current time window for intravenous tPA. Intra-arterial thrombolysis or mechanical clot retrieval may be alternative approaches for selected patients who do not respond to tPA within 3 hours, or within later time windows.<sup>11</sup> Thrombolysis is based on the recanalisation of occluded arteries and reperfusion of the ischaemic penumbra, a region of injured brain that is potentially salvageable with rapid restoration of blood flow. Identification of the penumbra using magnetic resonance imaging or perfusion CT may also allow individualised therapy at longer windows.<sup>12</sup> In 2007, we do not recommend routine use of intravenous tPA beyond 3 hours, but strongly encourage Australian clinicians to enrol patients into trials addressing these hypotheses.

Intravenous tPA is relatively simple to use, particularly with an effective partnership between emergency physicians and stroke clinicians, using appropriate protocols and stroke unit care. It is highly effective and relatively safe. In the 12 years since it was proven, the major systems failure in most countries has been delivering it to more patients. In Australia, we should not shirk from this challenge.

**Competing interests**

Stephen Davis has provided advice and given lectures on behalf of Sanofi-Aventis, Bristol-Myers Squibb, Pfizer and Boehringer Ingelheim. He is on the steering committees for Novo Nordisk, and SAINT (AstraZeneca) trials. Peter Hand is a member of the Boehringer Ingelheim National Advisory Board, and has received honoraria for various talks from Boehringer Ingelheim, Sanofi-Aventis, Pfizer, and Bristol-Myers Squibb. Geoffrey Donnan has provided advice to a number of pharmaceutical companies as a member of scientific advisory boards and has received honoraria for various presentations at international scientific meetings.

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