Thrombolysis for stroke: pushed out of the window?

Stroke remains the third largest cause of mortality in the Western world and the largest single medical cause of disability, yet after 40 years of clinical trials we still lack effective acute treatment. Thrombolysis has been a tantalising possibility, since 85% of strokes are caused by atherothrombotic arterial occlusion. If perfusion can be restored then it may be possible to salvage the region known as the ‘ischaemic penumbra’, brain tissue on the periphery of an infarct with sufficient collateral supply to remain viable for some hours after stroke onset: exactly how long the window of opportunity for intervention might be is unknown, with extrapolation from animal studies pushing most investigators towards short time windows. Natural reperfusion improves outcome [1] and a 1992 meta-analysis [2] suggested that thrombolytic drugs might do the same. Stroke physicians hoped that five large multicentre trials of thrombolysis (Table 1) would confirm these findings.

Unfortunately, the trials show that thrombolysis is dangerous for the majority of patients with stroke. The danger is due to a nemesis, hoped to have been banished by pretreatment computed tomography (CT) of the brain, intracerebral haemorrhage. A large excess of intracerebral haemorrhages after thrombolysis increased early mortality in all four trials with time windows over 3 h (although in ECASS the mortality increase did not quite achieve statistical significance). The odds ratio for death with treatment in these trials was 1.83. Increased early mortality outweighed possibly improved outcome in the survivors, evident in several of the trials.

Time appears to be the critical factor. Alone amongst the current trials, the increase in intracerebral bleeding in the NINDS trial did not translate into excess mortality. Despite rather conservative disability endpoints, NINDS found improved 3 month outcome with rTPA given up to 3 h after stroke.

Can the hazard of thrombolysis after 3 h be attributed to treating ‘the wrong patients’, as many stroke trialists would like to think? The ECASS results suggest that this may be so. Since large cerebral infarcts carry a greater risk of spontaneous haemorrhagic transform-

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Table 1 Multicentre thrombolytic trials in stroke

MAST-E signifies Multicentre Acute Stroke Trial-Europe; ASK, Australian Streptokinase Trial; ECASS, European Cooperative Acute Stroke Study; and NINDS, National Institute of Neurological Disorders and Stroke.

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Editorial for 'megatrials' with a 6 h window [3] is unethical until K. W. MUIR
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for 'megatrials' with a 6 h window [3] is unethical until there is evidence to support the safety of administration this late: there must be considerable doubt that further trials with 4 or 6 h windows will produce anything other than a larger body-count unless some fundamental change in the protocols is envisaged. The argument that patients with hemisphere strokes should be offered thrombolysis in 6 h window trials (and on present evidence, this means a trade between high immediate risk of death against a possibly increased chance of independence at 3 months) ignores the neurological deficit of these patients. If a patient with stroke is deemed competent to make such a decision, then their stroke is probably insufficiently severe for the question ever to be raised.

The future of thrombolysis may lie in combination with neuroprotective agents, but combination trials remain some way off. No neuroprotective drug has yet shown benefit in stroke, and several promising agents (e.g. selrotel, tirilazad, 619C89) have fallen by the wayside, at least temporarily. The safety of most of these drugs in intracerebral haemorrhage has never been explored, but is crucial if they are to be combined with a class of drugs known to provoke bleeding. It is also uncertain whether protection of the penumbra could avoid catastrophic haemorrhage into already infarcted central zones of dense ischaemia. Whilst a few animal studies have suggested benefits of combined thrombolysis and neuroprotection [4,5], the critical issue is whether the time window can be extended by the use of neuroprotectives, and animal models have been of very limited value in this respect. More preclinical data and clinical experience with neuroprotectives in intracerebral haemorrhage are required.

The attachment of investigators to thrombolytic drugs will ensure that further data are produced, and rtPA will no doubt be used in a minority of patients. The clear hazard to patients means that thrombolysis is unlikely to be favoured over any drug which is safe and even moderately effective; most of the neuroprotectives currently being developed hold this promise. The window for safe thrombolysis is likely to prove too small for most patients to squeeze into, and too hazardous to open if there is any alternative.

References
1 Baird AE, Donnan GA. Prognostic value of reperfusion during first 48 hours of ischaemic stroke. Lancet 1993; 342: 236.

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