Kissimmee, Florida, February 2006) suggest that the Merci procedure is also safe and effective in failed thrombolysis patients. The Merci procedure is currently being performed in over 150 centres in the US. It is estimated that over 3,000 patients have been treated with the device to date.

DANIEL BERECZKI

## *Evidence based thrombolysis*

Department of Neurology, University of Debrecen, Debrecen, Hungary

Evidence Based Medicine is a method of decision making when we decide which option is the best for a given patient in a given situation by considering the most reliable scientific evidence from clinical research. The level of scientific evidence depends on the amount and the quality of research data regarding the intervention in question. Systematic reviews of randomized controlled trials give the strongest scientific evidence.

Atherothrombotic disease may affect several organs, like the brain, the heart and the lower extremities causing ischemic stroke, myocardial infarction or gangrena of the extremities. To dissolve the occluding clot, i.e. thrombolysis may save the ischemic tissue from permanent damage, therefore seems to be a promising approach to treat atherothrombotic diseases. Thrombolysis may have other indications like pulmonary embolism, deep vein thrombosis of the extremities and there are some possible neurological applications like acute ischemic stroke, intraventricular hemorrhage, intracerebral hemorrhage and cerebral sinus/deep vein thrombosis.

Based on Cochrane reviews, thrombolysis may be beneficial in deep vein thrombosis of the lower extremities, but the optimal drug, dose and route of administration has to be determined in future trials. There is not enough evidence to decide if surgery or thrombolysis is better to treat acute limb ischemia. A meta-analysis of randomized controlled trials did not find enough evidence to decide if thrombolysis or heparin treatment is better for patients with pulmonary embolism.

Of the possible applications in central nervous system (CNS) disorders, there is no available evidence from randomized trials regarding the efficacy and safety of thrombolytic therapy in dural sinus thrombosis. There are only cohort studies describing rtPA or urokinase use in intraventricular or deep cerebral hemorrhages. Most trials in CNS disorders were performed in ischemic stroke and the Cochrane review of Wardlaw et al (2003) gives the best overview: thrombolytic treatment resulted in significant net reduction in death and disability, in an increase in death, and an increase in hemorrhagic complications. The outcome seemed better with earlier application and if rtPA was the thrombolytic agent.

rtPA has been licensed for intravenous use in patients within 3 hours of stroke onset. The currently ongoing IST-3 trial will help to decide several unsettled issues, like the possible expansion of the 3-hour time window, inclusion of people over 80 years of age, and those with mild and severe stroke signs.

PETER SANDERCOCK

## *Use of thrombolysis outside the 'classical' indication: should we or shouldn't we?*

Western General Hospital, Department of Clinical Neurosciences, Edinburgh, UK

It is now 12 years since the publication of the modest-sized 624-patient National Institute of Neurological Disorders and Stroke (NINDS) trial of iv rt-PA, that led to the FDA approval in 1996 of thrombolysis. As thrombolytic therapy is one of the very few effective treatments for acute stroke, wider implementation would be desirable. Yet, there is a major mismatch between expert opinion and guidelines (which support thrombolysis for selected patients within 3 hours of onset) and clinical practice. rt-PA for stroke has not been widely implemented in clinical practice; large-scale surveys suggest only 1-2% of stroke patients in developed countries receive it. Two factors are responsible in part for the poor implementation: the paucity of data on the effects of rt-PA treatment in many categories of stroke patients, especially the elderly and those who present more than 3 hours after onset; and the continuing debate over the evidence under-pinning licensed use (e.g. Australian Emergency Medicine physicians have refused to endorse the current Australian Governmental approval for rt-PA treatment for stroke because of ongoing debate over the trial data). Unless additional trial evidence establishes benefit for a wider variety of patients outside the current licence, especially among the elderly, the implementation – and public health impact - of this treatment will remain very limited.

The large European non-randomised post-marketing surveillance register of rt-PA, SITS-MOST, has showed an extraordinarily large 40-fold variation in use between the countries studied, from Finland, where 200 stroke patients per million population were treated with thrombolysis to 6 per million in France (SITS-MOST website http://www.acutestroke.org/, accessed 29/1/2007). More detailed surveys have confirmed that the proportion of all ischaemic strokes receiving thrombolysis remains small and variable worldwide: in the UK and Australia it is less than 1%; in the USA, Medicare data suggested about 2% were treated and a large-scale audit in US community hospitals confirmed variation between centres (0-5% treated); in Germany the proportion is about 3% (with centres treating between none and 18% of cases). Of course, there are exceptions; some stroke centres in USA and Europe manage to treat 10-20% with thrombolysis, but these are the exception rather than the rule. These figures contrast markedly with myocardial infarction where, as the resoundingly conclusive large scale studies, ISIS-2 and GISSI, led to a rapid change in practice, such that 40-60% of patients with acute myocardial ischaemia now receive prompt reperfusion therapy.

The total number of patients included in trials of rt-PA for stroke, the only approved drug for stroke thrombolysis, is a paltry 2830 patients. The licence for use within 3 hours of onset is based on evidence from just 960 patients. In the recommendations for research in the 2007 UK Government (NICE) appraisal, it states: 'Research is currently ongoing to evaluate the clinical effectiveness of alteplase beyond 3 hours after the onset of stroke symptoms (ECASS III and IST-3 studies). In addition, studies in patients older than 80 years would allow assessment of the clinical and cost effectiveness of alteplase in this population, which represents a significant and increasing proportion of the patients who experience acute ischaemic stroke. Use of alteplase in both of these settings is not within the drug's marketing authorisation. The ECASS-3 trial is only assessing the effects of rt-PA in those aged under 80 who present between 3 and 4.5 hours of onset; its results are expected in September 2008. However, it will not add any data on effects within 3 hours, 4.5-6 hours or in patients aged >80. Once ECASS-3 is completed, IST-3 will be the only trial comparing thrombolysis with control and hence represents the last opportunity to obtain randomised evidence on the effect of rt-PA in several important categories of patient. Given the current debate about who benefits from treatment 0-3 hours, and uncertainty about the balance of risk and benefit in the 3-6 hour time window, new data in this area will be essential to clarify the role of treatment. De Keyser has recently reviewed the clinical categories of stroke patients in whom there is clearly a need for further randomised data. IST-3 will contribute data on the main categories of patients identified in that review (more details available at www.ist3.com)

In summary, then, there is insufficient randomised evidence to guide the use of thrombolytic therapy outside the current license (the classical indication). If we are to obtain reliable (randomised trial) evidence which patients should be treated outside the current classical indication, the question will be answered more rapidly if patients in whom the treatment is considered 'promising but unproven' are treated in the context of a randomised trial such as IST-3.

Phrased differently, when faced with a patient whom you consider thrombolysis, but does not meet the criteria for the current EU approval, the question is not 'should we or shouldn't we (treat)', but 'can we randomise this next patient in a suitable trial'

DAVID ŠKOLOUDIK

## *Thrombolysis enhanced by sono-thrombotripsy*

Department of Neurology, University Hospital, Ostrava, Czech Republic

Since the 1970's, in vitro and animal models studies demonstrated acceleration of thrombus dissolution (clot lysis) using the ultrasound (US). Various US energies (0.2 – 2.0 W/cm2) and frequencies (20 kHz – 1 MHz) were used in these studies. High-intensity US at lower frequencies has primarily mechanical effects with a rapid disruption of clots into microscopic fragments and, at higher frequencies it can enhance enzymatic thrombolysis.

Alexandrov et al. (2000) reported a higher number of middle cerebral artery (MCA) recanalizations in patients treated with rt-PA IV than expected when transcranial Doppler (TCD) monitoring with a 2 MHz probe was used. In 2004 an open label randomized TCD study CLOTBUST showed a higher number of early recanalization of middle cerebral artery or dramatic recovery in patients treated with a combination of systemic thrombolysis with 2-hour TCD monitoring. In the last yeas, few studies reported that sono-thrombolysis using non-diagnostic TCD probe (300kHz) had a very high number of intracranial bleeding.

Skoloudik et al. (2003) and Eggers et al. (2004) reported first results with sono-thrombotripsy (TCCS monitoring of occluded MCA) in patients unable to treat with thrombolysis. The case-control multicenter Thrombotripsy study confirmed a potential therapeutical effect of trancranial Doppler monitoring in patients with MCA occlusion. In the Thrombotripsy group, 19 patients (36.5%) had complete recanalization and 27 (51.9%) patients had partial recanalization at one hour