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

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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

after the start of the TCCS monitoring. Higher recanalization rates at 6 and 24 hours after stoke onset were also seen compared to controls (69.2% vs. 7.7% and 92.3% vs. 61.5% complete recanalizations resp., $p < 0.05$). Independence (mRS 0-2) at day 90 was achieved by 61.5% of the Thrombotripsy patients and 32.7% controls, $p < 0.05$, OR 1.88 (95% CI = 1.23 – 2.90). In both groups, 2 symptomatic intracerebral hemorrhages and 1 symptomatic brain edema occurred.

In our last study, we monitored the changes in haemocoagulation parameters in 10 healthy volunteers after a thrombotripsy with 1-hour transcranial Doppler (TCD) monitoring.

After a thrombotripsy of the MCA, PAI-1 antigen, tPA antigen, fibrinogen, and AP activity were significantly decreased in 9 of 10 volunteers by a mean of 32, 23, 7, and 4% respectively ($p < 0.05$ in all cases), with normalization of values during the ensuring 24 hours. After a thrombotripsy of the RA, there was a significant decrease in tPA antigen alone by an average of 14% ($p < 0.05$). The time of ECL was prolonged by 15.2% ($p = 0.05$) 24 hours after thrombotripsy of the MCA. No changes in the levels of the other measured factors were detected. Standard NSE did not affect any of the measured factors.

MARTIN DENIS

Prevention of venous thromboembolism after stroke

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Deep vein thrombosis affects a significant minority of acute stroke patients in hospital. It may be complicated by pulmonary embolism which is one of the most important preventable causes of death after stroke. Prophylactic treatment which reduce the risk of DVT, and therefore presumably pulmonary embolism, should be offered in all stroke units. However, it is far from clear what those treatment should include. There are wide variations in the prophylaxis offered between units. Such variation is important since it suggests that many patients may be receiving suboptimal care and thus are exposed to an unnecessarily high risk of venous thromboembolism. Prof Martin Dennis will discuss the policies and the evidence for them.

ALE ALGRA

An update on secondary stroke prevention with antithrombotic drugs

University Medical Centre Utrecht, Netherlands

The presentation will be twofold: on secondary prevention after cerebral ischaemia of arterial origin (CIAO) and a cardiac source (CICO). The major trial after CICO is the EAFT that showed the superiority of mild oral anticoagulation (INR 2-3) over aspirin and placebo. Despite several more recent trials (e.g. SPORTIF and ACTIVE-W) the current standard remains mild anticoagulation. After CIAO several trials tried to improve the 13% relative risk reduction achieved with aspirin. Attempts with oral anticoagulation were disappointing: high INRs were not safe (SPIRIT), low INRs not effective (WARSS) and with a mild regimen (INR 2-3) the benefits for ischaemic events were cancelled by more major bleedings. Clopidogrel tended to be modestly more effective than aspirin after stroke (CAPRIE), but its combination with aspirin appeared to be not safe (MATCH, CHARISMA). Combination of aspirin with dipyridamole, however, appeared to be safe and to be more effective than aspirin alone (ESPS-2, ESPRIT). A recent update of guidelines of the American Heart Association now recommend the combination of aspirin and dipyridamole over aspirin alone.