Thrombolysis with alteplase after stroke: extending outcomes

In their first report since publication of the main results, the third International Stroke Trial (IST-3) investigators provide new data on the effects of alteplase on health outcomes after stroke, and so re-ignite debate about the best time and method to assess recovery.

90 days is the gold standard time for assessing the effects of treatment in acute stroke trials. This window provides a compromise between timely assessment of adverse effects and physical recovery and avoidance of the additional costs and logistic difficulties of longer follow-up. 18 month follow-up in the IST-3 study has several benefits. First, finding no difference in overall mortality (35%) between the groups provides reassurance that alteplase has no long-term adverse consequences related to restenosis of incompletely recanalised intracerebral arterioles. However, the data also suggest that any reduced neurological deficit from treatment did not translate into a net improvement in medium-term survival. Second, at 18 months, the proportion of patients who were alive and independent was significantly higher in the alteplase group compared with the control group (adjusted odds ratio [OR] 1·28, 95% CI 1·03–1·57; p=0·024). This difference was not evident in either the full cohort (1·13, 0·95–1·35; p=0·181) or at 6 months in the participants who were followed up for 18 months (1·18, 0·97–1·45; p=0·10). The consistent between-group distribution of scores on the Oxford handicap scale at 6 months and 18 months suggests that the treatment effect was stable but also shows some limitations to the approach.

The Oxford handicap scale score is based on several broad, ordered levels and so it is somewhat insensitive to change over time, can exhibit ceiling or floor effects, and is limited in its assessment of the functional consequences of stroke on the lives of those affected. As a result, health-related quality of life measures are recognised as valid and useful additional endpoints in randomised controlled trials, particularly for treatments that target chronic or disabling diseases. Indeed, medical decision-making increasingly focuses on health-related quality of life as an important variable because many treatments do not cure disease and patients often have an active role in their medical care and are particularly interested in the non-clinical aspects of treatment and their future requirement for care. EuroQoL is a popular generic, preference-based, measure of health-related quality of life because it is simple, concise, and efficient; it is also able to convert health effects into quality-adjusted life-years for evaluations of cost-effectiveness.

The large sample size in the IST-3 study (2348 patients assessed at 18 months) overcomes potential biases introduced through the use of proxies (in 54% of patients) to assess health-related quality of life. The findings from the EuroQoL instrument are therefore not only robust, but also offer separate confirmation of the functional benefits of alteplase besides the results of the Oxford handicap scale score. Additionally, they show that recovery from ischaemic stroke continues beyond 6 months—in the patients followed up at 18 months, only ability to self-care and ability to do usual activities were significantly improved at 6 months in the alteplase group. The difference between groups in overall health utility score also increased between 6 months and 18 months (from 0·04 to 0·06). Although this change is small, scores ranging from as little as −0·01 to 1·4 are still clinically meaningful. Finally, half of all participants reported at least a moderate degree of
P-glycoprotein expression and antiepileptic drug resistance

One of the most frustrating aspects of treating people with epilepsy is the inability to predict who will respond to antiepileptic drugs and who will be treatment resistant. Many theories of treatment resistance have been proposed, including association with disease severity and cause, genetic predisposition, changes in drug targets in the brain, aberrant drug metabolism, and even previous drug exposures during epileptogenesis, all of which could contribute to drug response. Whatever the cause, an individual who has shown resistance to one antiepileptic drug at a reasonable dose has a high likelihood of showing resistance to multiple drugs. In a study of 1098 newly diagnosed patients, failure of the first antiepileptic drug, at 50% or more of the WHO-defined daily dose, predicted pharmacoresistance in more than 70% of patients.

Upregulation of P-glycoprotein is one mechanism that might account for resistance to multiple antiepileptic drugs. Since many such drugs are substrates of P-glycoprotein, including commonly used treatments such as phenytoin, phenobarbital, lamotrigine, levetiracetam, topiramate, and carbamazepine-epoxide, the overexpression of P-glycoprotein could account for multidrug-resistance. In this issue of The Lancet Neurology, Maria Feldmann and colleagues provide the first in-vivo human evidence of the association between P-glycoprotein overactivity and pharmacoresistance in temporal lobe epilepsy. This was accomplished by looking at differences in PET studies with the P-glycoprotein substrate (R)-[11C]verapamil (and in some cases comparing before-and-after infusion of the P-glycoprotein inhibitor tariquidar) in 14 patients with pharmacoresistant temporal lobe epilepsy, eight seizure-free patients, and 13 healthy controls, and showing that the treatment-resistant patients had apparent higher baseline P-glycoprotein activity focally in regions of the hippocampus and temporal lobe.

Upregulation of P-glycoprotein potentially fits into many of the hypotheses to explain drug-resistance. There has been speculation that some individuals might have a genetic predisposition for increased expression of P-glycoprotein, due to a polymorphism in ABCB1, the P-glycoprotein transporter gene, which could lead to pharmacoresistance. However, as long as this overexpression occurs throughout the CNS, these individuals might also be expected to have resistance to side-effects involving the CNS, since less of the drug would reach its target. A second scenario is that some causes of epilepsy also produce an upregulation of P-glycoprotein, and in this case upregulation could...