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Conclusion

The repeated failure of almost all acute stroke trials to produce reproducible evidence of clinical benefit means that patients continue to suffer hopelessly from cerebral infarction, and the health professionals in charge of them remain in great need of therapeutic progress.

For a few therapeutic approaches, partial, preliminary, subgroup or pooled data suggest that some benefit can be expected. Among the neuroprotectants, nimodipine, a calcium antagonist of the dihydropyridine class had positive results found only in a subgroup treated early (12 h from onset) in a meta-analysis of 9 trials [1]; citicholine only had positive results in a post hoc defined subgroup (unpubl. data); lubeluzole was positive in a secondary endpoint in one study (Lub-Int 5) and positive only in a subgroup in another study (Lub-Int 9); piracetam had a positive result only in a subgroup treated early (less than 6 h), particularly if patients with mild impairment were excluded [2].

Among thrombolytics, i.v. urokinase was tried only in a few small trials, with apparently very unfavorable results, and by intra-arterial administration in open studies with some encouraging results. Streptokinase was used in a number of small series, with quite diverse outcomes and in three reasonably large size trials (MAST-E [3], MAST-I [4] and ASK [5]). All of them showed an excess of death in the treated group, which either balanced or outnumbered the number of patients with a better functional outcome, so that the net result ranged from neutral to unfavorable. Two large trials with intravenous tissue-type plasminogen activator (t-PA) yielded conflicting results on mortality: the ECASS trial [6] concluded that there was an increase in mortality in the group treated with 1.1 mg/kg during the first 6 h after stroke onset, while the NIH t-PA study [7] found a slight reduction in mortality in patients treated with 0.9 mg/kg i.v. within 3 h of a stroke. In both trials there was a reduction in the number of patients with significant sequelae, which was balanced out by the excess number of deaths in the ECASS, but resulted in a net statistically significant benefit in the NIH trial. As a consequence, this treatment was approved by the FDA in the United States, but still very few stroke patients are treated with

t-PA in the United States (less than 2%) because of the logistic constraints and the fear of hemorrhagic complications. In other countries recombinant t-PA is either not given in acute ischemic stroke or even contraindicated (in France), pending a second positive trial.

As, altogether, the repeated functional benefits of systemic thrombolysis in published trials were canceled out (or worse) by an excess mortality due to cerebral hemorrhage, there is an obvious need for an approach which would provide the benefit without the risk. As presented at this symposium this could be achieved by a combination of a better selection of patients, better designs of trials and the use of safer drug. From the evidence presented it seems that Ancrod might be such a drug; the results of the two pivotal phase III ongoing trials are, therefore, awaited with much interest and hope.

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