New Approaches to Clinical Trials in Neuroprotection

Introduction

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In 10 years after the US Food and Drug Administration’s approval of intravenous tissue plasminogen activator (tPA) for acute ischemic stroke, tPA has had only a modest impact in the overall burden of disease. Current estimates suggest that about 2% to 8% of US ischemic stroke patients receive tPA,1 and that continuing improvement of in-hospital care might not increase this proportion much beyond 20%.2 There remains an urgent need for additional therapeutic approaches to acute ischemic stroke. Neuroprotective drug strategies offer the promise of limiting infarct tissue damage without increasing hemorrhage risk. Despite an extensive literature showing neuroprotective drug actions in reducing infarct size in rodent ischemia models, efficacy has not been confirmed in large multicenter clinical trials.3,4 This situation is not unique to neuroprotective agents because many promising recanalization approaches have also failed. For example, a large trial of the glycoprotein IIb/IIIa inhibitor, abciximab, administered within 5 hours of symptom onset (or 3 hours after awakening with stroke) was recently terminated because of concerns of increased risk of intracranial hemorrhage in the treatment group.5 The defibrinogenating agent, ancrod, did not improve stroke outcome when administered within 6 hours of symptom onset (ESTAT study) although it was found effective within 3 hours of onset in a previously reported trial with otherwise similar design (STAT study). The parallel experience with clinical trials of tPA and ancrod serves to highlight the importance of early stroke recognition and rapid drug administration. No intravenously administered recanalization agent has been proven effective beyond 3 hours after onset, and no neuroprotective agent has even been tested within this time window. Considering the number of negative studies, and the persisting difficulties of very early patient recruitment, industry and public sponsors are understandably wary of the commitment required for new acute intervention trials. The NIH-funded NINDS tPA trial cost more than $18 million (scaled to 2004 US dollars) and current industry-sponsored stroke trials are likely much more expensive. What are the prospects for future development of effective stroke therapies? This Princeton session examined the challenges from two perspectives: improving therapeutic options and improving trial methodologies.
some come with costs of increasing statistical assumptions or uncertainty in trial planning. Dr Tilley described new consortia established by NINDS to Parkinson’s Disease clinical research: the Committee to Identify Neuroprotective Agents for Parkinson’s (CINAPS), and Neuroprotection-Exploratory Trials in PD (NET-PD). Standing clinical trial collaborations have long served the cardiology, cancer, and AIDS research communities, and there are important lessons here for stroke and neurodegenerative diseases.

Acute intervention trials for stroke are undeniably costly, but it is important to consider these costs in the context of the much larger personal and societal economic burden of the disease itself. A recent analysis compared the costs and public health benefits of all 28 phase III clinical trials supported by the NINDS between 1977 and 2000. The total cost of funding these trials was $335 million (measured in 2004 dollars). The economic benefit was estimated at over $15 billion over 10 years. We can build better clinical stroke trials; we can’t afford not to.

References

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