Use of Animal Models Has Not Contributed to Development of Acute Stroke Therapies

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The development of therapies for acute ischemic stroke (AIS) has proven to be a difficult and challenging endeavor, reflecting the complexity of the pathophysiology and clinical aspects of this heterogeneous disorder. With only one currently approved therapy for AIS, tPA initiated within 3 hours of stroke onset, there is only a limited track record to assess the use of animal models in the development of AIS therapies. A negative perspective can be taken that a large number of interventions demonstrated efficacy in animal models of AIS and these interventions, primarily neuroprotective agents, have not been shown to improve AIS outcome in patients. This pessimism about the value of animal models for providing help in the development of AIS therapies must be viewed cautiously because there are many reasonable explanations for the lack of translation of therapeutic benefit in animal stroke models into successful clinical trials. The potential reasons for lack of translational success were previously well summarized and reflect problems both in how animal modeling was conducted to assess therapies and also how clinical trials were performed. The Table provides an overview of these contentious issues.

The potential use of animal models for helping to develop AIS therapies should be viewed from several perspectives. It is now widely appreciated that the pathophysiology of tissue injury in AIS is at once both simple and complex. Simple in that the intraluminal blood flow compromise induced by a thrombus or embolus initiates an increasingly complex array of potential contributory mechanisms of cellular and subcellular injury that vary depending on the level of blood flow compromise, the metabolic milieu, genetic environment, and other confounders. Animal modeling has certainly contributed to our understanding of these mechanisms of ischemic injury and helped to identify potential therapeutic targets for new interventions currently being tested in clinical trials. Additionally, animal models provide a mechanism to evaluate the temporal and spatial evolution of ischemic brain injury using advanced imaging techniques such as diffusion/perfusion magnetic resonance imaging (MRI), and these techniques can then be adapted to patients with AIS to evaluate these same characteristics. The idea of the ischemic penumbral injury in AIS is at once both simple and complex. Simple in that the intraluminal blood flow compromise induced by a thrombus or embolus initiates an increasingly complex array of potential contributory mechanisms of cellular and subcellular injury that vary depending on the level of blood flow compromise, the metabolic milieu, genetic environment, and other confounders. Animal modeling has certainly contributed to our understanding of these mechanisms of ischemic injury and helped to identify potential therapeutic targets for new interventions currently being tested in clinical trials. Additionally, animal models provide a mechanism to evaluate the temporal and spatial evolution of ischemic brain injury using advanced imaging techniques such as diffusion/perfusion magnetic resonance imaging (MRI), and these techniques can then be adapted to patients with AIS to evaluate these same characteristics. The idea of the ischemic penumbral, initially suggested by animal studies, is central to the therapeutic time window concept that is being exploited to develop AIS therapies that potentially can be effective at later time points, as exemplified by the Desmoteplase MRI-based preliminary trial. It is only with the availability of increasing knowledge about AIS pathophysiology and temporal evolution provided by animal models that novel therapies at increasingly delayed time points can be developed.

Using animal stroke models for the development of AIS therapies in the future should be approached carefully and rigorously. It must be recognized that no animal stroke model will precisely mimic human AIS, a condition that is quite heterogeneous. Recognizing the inherent limitations of animal stroke modeling should provide important lessons for both basic and clinical stroke researchers. Animal modeling-based treatment experiments must be performed to answer specific, goal-oriented questions. Choosing the most appropriate experimental conditions to address questions about a drug’s therapeutic time window, dose–response relationship, and side effect profile should provide valuable information to help in the design of subsequent clinical trials. If a drug has a short time window in a model with a well-characterized time period of penumbral survival and a narrow therapeutic index of efficacy to safety, then it is unlikely that the agent represents a good candidate for clinical development. Animal studies should be used to predict likely futility to eliminate drugs not likely to succeed in clinical trials, as well as to identify favorable drugs that should proceed to clinical development. Initial suggestions that are now widely used by the pharmaceutical industry for a preclinical assessment paradigm for novel AIS therapies were made by the STAIR group in 1999 and recently expanded on. Conversely, a favorable therapeutic profile in stroke models does not guarantee success in clinical development, especially if the clinical trial program repeats the flawed approaches used to assess many drugs in the past. As AIS therapy development evolves toward combination approaches, the performance of good preclinical studies will assume increasing importance to help determine optimal dosing regimens for maximal efficacy and to evaluate the potential for interactions among the drug
Potential Problems With Prior Animal and Clinical Studies for Acute Stroke Therapies

Animal Studies
1. Studies used healthy, young animals without comorbid conditions
2. Animal experiments were performed under anesthesia and involved a surgical procedure to induce arterial occlusion
3. The occlusion did not involve a clot
4. Physiological parameters were not well-controlled
5. Studies were not done in a strictly randomized, double-blind fashion
6. Prolonged survival studies were not performed to document a persistent treatment effect
7. Histology was the primary outcome and treatment effects on sophisticated functional outcome measures were not performed
8. Drug treatment was started before induction of ischemia or very early after that at a time point not relevant to the clinical condition
9. Adverse effects of novel neuroprotective agents may have been overlooked

Clinical Studies
1. An appropriate time window was not used based on preclinical data
2. Adequate drug levels were not achieved because of toxicity
3. The mechanism of drug action was not considered in the trial design, ie, drugs with no effect on white matter injury included patients with lacunar stroke
4. Outcome assessment of a therapeutic response was not adjusted for baseline severity
5. The outcome assessment was not adapted to the mechanism of drug action
6. The trial included too many mild or severe patients
7. Many clinical trials were initiated on the basis of insufficient preclinical data
8. Insufficient statistical power
9. Protocol violations

combinations. These issues will be critical for helping to determine how to best initiate clinical trials.

The field of AIS therapeutics has been littered with many failures and only rare successes. To blame animal stroke modeling as a primary culprit for these failures may be convenient but not accurate. In fact, the narrow therapeutic time window observed with most neuroprotective drugs may actually have predicted the lack of efficacy observed with these agents in clinical trials in which most patients were treated 5 to 6 hours or longer after stroke onset.10 Going forward, information from animal modeling should be heeded and the lessons learned incorporated into clinical trial design. It is entirely likely that the combination of improved preclinical assessment and clinical trial design/implementation will conjointly expedite the development of novel AIS therapies.

References

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