In the beautiful archipelago of Stockholm, there was a satellite symposium in connection with the World Congress of Medicine in 1980. The role of calcium was then a hot topic in the cerebral ischemic cascade. A paper presented at the symposium demonstrated that a calcium blocker was able to decrease the size of brain infarction in rats. Already then I had a few reservations about such experimental models. In a laboratory, an investigator can modify all known confounding factors and the time from onset of ischemia to the administration of an experimental drug. The body temperature, blood pressure, blood glucose, and acid-base balance of animals can be kept constant and within normal physiological ranges. In a busy emergency room, where an elderly stroke patient is admitted with many severe concomitant diseases, ie, fragile diabetes, untreated hypertension, recent myocardial infarction, and imminent heart failure, the treating physician has major problems in balancing them while the time from onset of symptoms is, at best, an educational guess. I pointed out my doubts and asked whether the treatment would have an equal efficacy in humans as it had in rats. There was no good answer. Twenty-four years later and the treatment would have an equal efficacy in humans as it had in rats. There was no good answer. Twenty-four years later and the treatment would have an equal efficacy in humans as it had in rats. There was no good answer. Twenty-four years later and the treatment would have an equal efficacy in humans as it had in rats. There was no good answer. Twenty-four years later and the treatment would have an equal efficacy in humans as it had in rats. There was no good answer. Twenty-four years later and the treatment would have an equal efficacy in humans as it had in rats. There was no good answer. Twenty-four years later and the treatment would have an equal efficacy in humans as it had in rats. There was no good answer. Twenty-four years later and the treatment would have an equal efficacy in humans as it had in rats. There was no good answer. Twenty-four years later and the treatment would have an equal efficacy in humans as it had in rats. There was no good answer. Twenty-four years later and the treatment would have an equal efficacy in humans as it had in rats. There was no good answer. Twenty-four years later and the treatment would have an equal efficacy in humans as it had in rats. There was no good answer.

Since the early days of neuroprotecting agents in treatment of acute stroke, more than 700 drugs have been studied and more than 4000 papers describing their neuroprotective efficacy have been published, and yet none of those drugs has been accepted by regulatory authorities to be used for treatment of patients with acute stroke in the United States or the European Union. There are many reasons for the failures and we are still on the learning curve, but is this endless optimism of the Village Idiot fruitful? The evidence from position emission tomography studies has revealed that without early reperfusion, either spontaneously or induced by thrombolysis, the size of the final brain infarction can only marginally be reduced with neuroprotecting agents because the critically hypoperfused area accounts for the largest proportion (mean 70%) of the final infarct volume. Accordingly, even if neuroprotectants could prevent the maturation of the ischemic penumbra to an infarct by half, like they do in animal models, it would only reduce the size of the final infarction by 15%. It would ask for a trial with tens of thousands of stroke patients to prove such a hypothesis. My estimation is based on the assumption that thrombolysis is superior to neuroprotectant therapy and the fact that thrombolytic trials with a longer than 3-hour time window have all failed. To be positive, thrombolytic trials in which IV rtPA was initiated within a 4.5- to 6-hour time window should have enrolled 4500 patients.

Have I learned anything else from taking part in clinical acute stroke trials based on drugs that have been found to be effective in animal models but to perceive many reasons for the failure of these trials? There is no doubt that I have gained lots of experience, which has improved the daily stroke patient care at our department. Without our participation in many neuroprotectant and thrombolytic trials, our stroke triage developed as part of these trials would certainly be less well organized. With lots of training, our present record of the door-to-needle time for rtPA is 12 minutes, which includes clinical examination, laboratory tests, computed tomography, and informed consent. Furthermore, we have enrolled more patients with stroke in the official register for rtPA-treated stroke patients, the SITS-MOST, than any other center in Europe.

Animal models have helped us better understand the pathophysiology of ischemic brain damage, but have they otherwise contributed much to clinical practice so far? I cannot say that they have, whereas randomized, clinical trials (RCTs) have had a major impact. The need of discipline, an essential part of any RCT, has influenced ordinary patient care in many positive ways. I do not expect either that more developed animal models could contribute to emergency stroke care so that a neuroprotective agent would be able to reduce the volume of an infarct in patients with stroke by 50% as they do in rats, at least if the therapy is not combined with thrombolysis or other neuroprotective therapies. If, however, one means by the use of animal models studies aimed at...
enhancing neuronal regeneration after acute stroke, the landscape changes to a truly bright one. Here the Holy Grail of clinical stroke therapies waits for those who are worthy. In an innovative animal model, Lee and colleagues presented strong data for cAMP response element-binding protein (CREB) family transcription factors in recovery from experimental hypoxic ischemic brain damage and that drugs can be used to enhance neuronal recovery. Their observations may open a highway not only for neuronal recovery and reorganization after stroke, but also in Alzheimer disease, spinal cord injuries, and in many other neurologic diseases, which now so desperately wait for breakthroughs.

References

Key Words: acute stroke [animal models]

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

Con

Marc Fisher, MD; Turgut Tatlisumak, MD, PhD

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 penumbra, 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

Received May 10, 2005; accepted July 13, 2005.
From the Department of Neurology (M.F.), University of Massachusetts Medical School, Worcester, Mass; and the Department of Neurology (T.T.), University of Helsinki, Helsinki, Finland.
Correspondence to Marc Fisher, MD, UMASS/Memorial Healthcare, 119 Belmont St., Worcester, MA 01605. E-mail fisherm@ummhc.org
© 2005 American Heart Association, Inc.
*Stroke* is available at http://www.strokeaha.org
DOI: 10.1161/01.STR.0000179039.76922.e8
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

The lack of efficacy with many drugs can often be explained by the narrow therapeutic time window observed with most neuroprotective drugs. 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. 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 jointly expedite the development of novel AIS therapies.

References


Key Words: acute stroke • animal models
Stroke Drug Development
Usually, But Not Always, Animal Models

Geoffrey A. Donnan, MD, FRACP; Stephen M. Davis, MD, FRACP

In 2005, the standard mode of drug development is to determine its biologic mechanism, efficacy, dosage, and time window in preclinical animal models. The only licensed acute pharmacologic intervention for stroke is tPA, which traveled this conventional route before proof of its efficacy in pivotal clinical trials.1 Many stroke clinicians have been perplexed by the failure of other compounds trialed over the past 2 decades, despite strong evidence for efficacy in animal models. Indeed, the specter of investigator fatigue is raised in the face of continued negative results, chiefly from trials of neuroprotectants.

Fisher nicely argues that there are many reasons why translation of neuroprotectants from animal models to clinical practice has not occurred and, indeed, this has been the theme of a series of STAIR recommendations. Our personal bias is that a large number of neuroprotectants have had inadequate preclinical testing in differing models, species, and appropriate time windows. For example, there is little justification for human studies of an agent that reduces infarct volumes in a single rat model by 30% with inappropriately short time windows.

As argued by Fisher, there is also often a poor understanding of the model itself; knowledge of the presence and duration of the ischemic penumbra is critical. Trial methodology has now become much more sophisticated, and negative results are more like to be the result of biologically weak compounds.2 In addition, treatment effect sizes are likely to have been overestimated, and we would not expect an absolute risk reduction of more than approximately 3% to 5% for neuroprotectants, substantially lower than for thrombolytic therapy. We are firmly of the view that larger sample sizes are required for these trials than are currently used.

One inescapable fact highlighted by Kaste is that the rigor of case selection and patient management in clinical trials has driven the standards of acute stroke care. This may be a factor in the lower-than-expected mortality rates in many trials. Also, such efficiencies may explain the impressive record door-to-needle time of 12 minutes from the center of our protagonist from Finland!

One striking exception to the conventional pathway of drug development has been the positive results using recombinant factor VIIa to attenuate hematoma growth in patients with primary intracerebral hemorrhage.3 The biologic plausibility of this approach was based on clinical studies of the dynamics of hematoma growth documented by repeated computed tomography scans rather than animal models. The compound was already in clinical use as a hemostatic agent for another indication. This illustrates our view that although the majority of candidate stroke compounds need to be evaluated in preclinical animal models, there is always a place for astute clinicians to recognize the potential of compounds already in use for another clinical indication.

Despite the recent history of failure of translation of neuroprotectants into clinical practice, promising trial results have been recently released for a free radical trapping agent. The development of this compound was based on a rigorous preclinical program, including multiple animal models and careful adherence to the STAIR criteria.4 This message should not be lost on investigators hoping for success in the tough world of translational stroke research.

References

Key Words: acute stroke I animal models

Received May 11, 2005; accepted May 18, 2005.
From the National Stroke Research Institute, Austin and Repatriation Medical Centre and University of Melbourne, Melbourne, Australia (G.A.D.); and the Department of Neurology, Royal Melbourne Hospital and University of Melbourne, Australia (S.M.D.).
Correspondence to Geoffrey A. Donnan, MD, FRACP, National Stroke Research Institute, Austin Health, Level 1, Neurosciences Bldg, University of Melbourne, 300 Waterdale Rd, Heidelberg Heights, Victoria, Australia 3081. E-mail gdonnan@unimelb.edu.au

Stroke is available at http://www.strokeaha.org DOI: 10.1161/01.STR.0000179042.06535.2f

2326
Use of Animal Models Has Not Contributed to Development of Acute Stroke Therapies: Con
Marc Fisher and Turgut Tatlisumak

Stroke. 2005;36:2324-2325; originally published online September 1, 2005;
doi: 10.1161/01.STR.0000179039.76922.e8

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/36/10/2324

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org//subscriptions/