Neuroprotection and Traumatic Brain Injury

The Search Continues

Alan I. Faden, MD

During the last decade, experimental studies of traumatic brain injury (TBI) have provided important new insights into the pathophysiological mechanisms leading to post-traumatic tissue damage and associated neurological dysfunction. The concept of delayed or secondary tissue injury has strong experimental support and a cascade of secondary injury factors has been delineated.\(^1,2\) These observations have led to the application of targeted pharmacotherapies, whose aim is to block specific pathobiological pathways.\(^2,3\) Such research has been aided by the development of rodent models of head injury that simulate critical components of clinical neurotrauma, as well as by the development of novel neuroprotective agents.\(^3,4\) These experimental studies have identified mechanisms of delayed tissue damage and have demonstrated the effectiveness of a number of pharmacological treatment strategies.\(^1-4\) However, despite this enormous experimental promise, the clinical studies to date have been disappointing.\(^5,6\) Here we explore the conceptual and methodological issues that have contributed to this discrepancy between preclinical and clinical studies.

SECONDARY INJURY AND NEUROPROTECTION: PRECLINICAL STUDIES

Although earlier studies focused on brain injury models in higher species such as the sheep, cat, and primate, most studies during the past decade have used rodent models.\(^7\) Such models have been designed to reflect certain components of clinical head injury, such as contusion, hematoma, and/or diffuse axonal injury.\(^6,7\) Nonetheless, there are significant questions as to how adequately these animal models reflect human brain injury, which is a highly heterogeneous disorder. Moreover, rat models generally use highly inbred strains of one sex in an effort to minimize intersubject variability. Despite these limitations, a variety of biochemical changes have been consistently identified across experimental models and across laboratories; these include changes in ionic homeostasis (calcium, potassium, sodium, magnesium), release of excitatory amino acids, induction of free radicals, inflammatory/immune changes, and alterations of multiple neurotransmitter systems.\(^1,2\) among others. It has also been established that TBI leads to apoptotic as well as necrotic cell death, and that both forms of cell death may be pharmacologically modulated.\(^8,10\) These observations have led to the evaluation of numerous pharmacological strategies, including calcium channel blockers, corticosteroids and other antioxidants, glutamate receptor antagonists, opioid receptor antagonists, thyrotropin-releasing hormone analogs, and magnesium administration, as well as various anti-inflammatory and immune modulatory treatments.\(^3,4\) Some of these approaches, such as the use of N-methyl-D-aspartate receptor antagonists, have particularly strong experimental support.\(^8,33\) More recently, it has also been shown that modulation of apoptotic cell death by inhibiting caspases also improves outcome after TBI.\(^9\) Another strategy that has gained increasing experimental support but that has not yet been
translated into well-designed clinical trials is the use of either combination therapies that block different components of the secondary injury cascade or administration of single agents (such as thyrotropin-releasing hormone or HU-211) that modulate multiple components of the cascade.\textsuperscript{12,13}

**NEUROPROTECTION AND TBI: CLINICAL STUDIES**

During the past 50 years, numerous clinical trials of neuroprotective agents have been conducted. In general, these have not shown significant beneficial effects.\textsuperscript{3,6} Negative trials have included evaluation of corticosteroids, barbiturates, calcium channel antagonists, antioxidants/free radical scavengers, and glutamate antagonists, among others.\textsuperscript{5,8,14,15} Why has it been so difficult to demonstrate effective drug treatments for clinical head injury in contrast to recent studies of stroke or spinal cord injury? Moreover, why are there such substantial discrepancies between animal head injury studies and related clinical studies? There are various potential explanations for such failures.

**HETEROGENEITY OF POPULATIONS BEING STUDIED**

As noted above, patients with severe brain trauma include a heterogeneous population with regard to underlying mechanisms of secondary injury, with the latter including varying degrees of hypoxia, ischemia, contusion, diffuse axonal injury, edema, and the presence of associated hematoma.\textsuperscript{8} Therefore, in evaluating potential therapeutic strategies, investigators may need to better define and stratify subpopulations of patients being studied. For example, although 2 earlier clinical trials of nimodipine treatment in head injury were negative,\textsuperscript{16,17} a subgroup analysis suggested a potential benefit in patients demonstrating traumatic subarachnoid hemorrhage. A subsequent small study that focused on patients with traumatic hemorrhage did report a significant treatment effect.\textsuperscript{18} The latter will need to be repeated with larger numbers of patients but it does suggest the possibility that clearer delineation of classes of patients with head injuries may increase the likelihood that significant neuroprotective effects may be observed.

**INJURY SEVERITY**

Clinical trials have generally included patients with severe head injuries. However, animal studies have shown that moderate head injury may provide a better target for evaluation of neuroprotective treatments. Subjects with severe injuries may be incapable of demonstrating a treatment effect because of the severity of the primary insult or associated injuries. On the other hand, inclusion of only mildly injured patients may lead to a ceiling effect, in which case it is unlikely that a treatment effect can be observed unless very large populations are studied.

**RELEVANCE OF ANIMAL MODELS**

Animal models are usually designed to model a component of clinical head injury, such as concussion or contusion, to improve consistency across subjects and reduce outcome variability. Despite inherent difficulties, it would be desirable to develop more complex animal models that may include hypoxia, ischemia, or other potentially relevant components of clinical head injury (hemorrhage, hematoma, etc).

**END POINTS**

End points in clinical and experimental studies often differ significantly. Experimental studies generally use behavioral assessment and lesion volume measurements, whereas clinical studies may examine combined death/disability or use surrogate markers such as intracranial pressure changes.

**TIME POINTS/THERAPEUTIC WINDOWS**

In experimental studies, pharmacotherapies are often administered either as pretreatment or as very early post-treatment (ie, 15-30 minutes). In contrast, clinical studies can rarely enter a brain trauma patient into a study sooner than 3 to 6 hours after injury, particularly in view of difficulties in obtaining informed consent. More clinically relevant treatment times should be examined in animal studies before they are moved into the clinic. It is also important to develop clinical treatment approaches that permit earlier treatment times.

**PHARMACOLOGY IN EXPERIMENTAL MODELS**

In animal studies, it is rare that pharmacokinetic or pharmacodynamic studies are performed. Moreover, studies examining central penetration of systemically administered compounds are rarely conducted. More detailed pharmacological profiles, as well as optimization of treatment protocols, should be conducted in animals before moving such studies into clinical trials.

**COMBINATION OR MULTIPOTENTIAL TREATMENT STRATEGIES**

Experimental studies have established that both necrotic and apoptotic cell death occur after TBI.\textsuperscript{8-10} Moreover, it has been shown that treatment strategies aimed at necrosis may enhance apoptotic cell death.\textsuperscript{19} Importantly, combination treatment with agents directed to each type of cell death have shown additive, if not synergistic, treatment effects.\textsuperscript{20} Further studies are needed to examine whether such combination treatment strategies can improve outcomes in more clinically relevant animal model systems.

**OTHER METHODOLOGICAL DIFFERENCES**

Another major difference between clinical and preclinical studies is that the former generally use an intent-to-treat methodology; that is, patients are included in the treatment group even if by mistake they did not receive the effective treatment dose. In contrast, with animal experimentation, investigators routinely exclude an animal that fails to receive adequate treatment; in many cases,
subjects are excluded based on other criteria, such as inadequacy of trauma, etc.

LESSONS LEARNED: CAN THEY BE APPLIED?

Many important lessons have been learned during the past few years regarding clinical trial design in head injury/neuroprotection studies. In many reported studies there has been concern about adequacy of sample size and some recent studies suggest substantial increases in proposed sample size. Future clinical studies should identify more appropriate target populations, ideally focusing on moderate as opposed to mild or severe injury. It will be important to better stratify these populations, for example, with regard to the presence or absence of significant hemorrhage or other confounding factors. Future trials should also await more complete preclinical investigation, in particular with regard to such issues as therapeutic window, pharmacokinetics, and central nervous system drug penetration. Finally, more emphasis should be placed on evaluating either drugs with multipotential treatment actions (ie, altering multiple components of the secondary injury cascade) or combination treatment strategies.

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Corresponding author: Alan I. Faden, MD, Department of Neuroscience, EP-12 Research Bldg, 3970 Reservoir Rd NW, Washington, DC 20007 (e-mail: fadenag@georgetown.edu).

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