Riluzole for Acute Traumatic Spinal Cord Injury: A Promising Neuroprotective Treatment Strategy

Jefferson R. Wilson and Michael G. Fehlings

Key words
- Mechanisms of spinal cord injury
- Riluzole
- Spinal cord injury
- Treatment

Abbreviations and Acronyms
ALS: Amyotrophic lateral sclerosis
NACTN: North American Clinical Trials Network
SCI: Spinal cord injury

INTRODUCTION
For years, the central mantra underlying the treatment of ischemic stroke has been that “Time Is Brain.” In recent years, it has become increasingly recognized that this same principle applies to the treatment of traumatic spinal cord injury (SCI) and that “Time Is Spine.” This phrase refers to the fact that there is a critical time window after the primary cord injury during which secondary injury mechanisms, which cause increased neural tissue damage and worsened clinical outcomes, can be averted. The current challenge is to identify and develop effective targeted therapies that can be practically administered during this critical acute time window (29). Studied acute therapies that have been shown to be effective at improving outcomes by mitigating secondary injury events include methylprednisolone sodium succinate administered in the first 8 hours after injury and decompressive surgery performed within the first 24 hours after injury (8, 9, 14).

Riluzole is a benzothiazole anticonvulsant drug that shows promise as an acute neuroprotective therapy for SCI (32). It is currently approved by the U.S. Food and Drug Administration for treatment of patients with amyotrophic lateral sclerosis (ALS). In the realm of SCI, riluzole has been shown to improve neurobehavioral and pathologic outcomes in injured animals through mitigating sodium-related and glutamate-related secondary injury mechanisms. A phase 1 clinical trial investigating the safety and pharmacokinetic profile of riluzole in SCI has been completed more recently. This article reviews the biologic rationale, existing preclinical evidence, and emerging clinical data for the use of riluzole in the treatment of traumatic SCI.

BACKGROUND: Over the years, understanding of the specific secondary injury mechanisms that follow traumatic spinal cord injury (SCI) has improved. These pathologic mechanisms collectively serve to increase the extent of neural tissue injury, reducing prospects for neurologic recovery. An enhanced understanding of the pathobiology of SCI has permitted investigation of therapies targeting specific elements of this pathologic cascade. It is now known that the continuous post-traumatic activation of neuronal voltage-gated sodium ion channels leads to increased rates of cell death through the development of cellular swelling, acidosis, and glutaminergic excitotoxicity. The objective herein is to provide an update regarding the current status of the potential neuroprotective drug riluzole in the treatment of traumatic SCI.

METHODS: Narrative review and summary paper.

RESULTS: Riluzole is a sodium channel–blocking benzothiazole anticonvulsant drug that is approved by the U.S. Food and Drug Administration for the treatment of amyotrophic lateral sclerosis and has shown efficacy in preclinical models of SCI in reducing the extent of sodium and glutamate mediated secondary injury. This drug is currently under early stages of clinical investigation in SCI and shows promise as an acute neuroprotective therapy in this context.

CONCLUSION: This article reviews the biologic rationale, existing preclinical evidence, and emerging clinical data for riluzole in the treatment of traumatic SCI.
the overall result being local tissue ischemia (31, 36, 37, 40). At a cellular level, the initial trauma and subsequent ischemic changes incite numerous additional pathologic events, including membrane peroxidation, free radical formation, ionic imbalance, and release of excitotoxic levels of the neurotransmitter glutamate (10, 18, 25, 27). The latter two mechanisms are reviewed in greater detail subsequently because these are particularly germane to the discussion of riluzole and its mechanism of action.

**Sodium and Glutamate–Related Secondary Injury**

There is robust laboratory evidence that neuronal intracellular sodium concentrations increase as a result of the pathologic constitutive activation of voltage gated sodium channels during the secondary injury cascade (Table 1) (3). This increase in sodium levels results in cellular swelling through reversal of the osmotic gradient and intracellular acidosis through increased entry of protons through the sodium proton exchanger (34). The increases in intracellular sodium also promote an influx of calcium ions through the sodium calcium exchanger, which triggers the excessive and pathologic extracellular release of the excitatory neurotransmitter glutamate (16, 17, 21, 26, 35). The end result is a potentiation of cellular death as a result of cytotoxic edema, intracellular acidosis, and glutaminergic excitotoxicity.

**PRECLINICAL EVIDENCE FOR USE OF RILUZOLE IN SCI**

Given that the posttraumatic pathologic activation of voltage-gated sodium channels has been identified as an important event contributing to increased cell death, blockade of these channels has been intensively studied as a therapeutic target within preclinical SCI models. In a series of in vitro electrophysiologic experiments from the Fehlings group, the neurophysiologic function of dorsal column axons isolated from adult rats were studied after clip-compression–induced injury, using microelectrode recording techniques (2). The authors determined that reduction in extracellular sodium concentrations improved function after injury, whereas increasing axonal membrane permeability to sodium led to reduced function. As a second step, the injured axons were superfused with a solution containing several different sodium channel–blocking compounds. The inclusion of these compounds led to improvements in electrophysiologic function over postinjury control recordings completed in the absence of these compounds. This study confirmed the detrimental effects of increased intracellular sodium on the function of injured neurons and provided an experimental rationale for investigating sodium channel blockade as a means of averting secondary injury after SCI.

Building on the in vitro work, numerous attempts have been made at establishing the in vivo efficacy of sodium channel–blocking compounds in animal models of SCI. Agrawal and Fehlings (1) showed that although administration of the local anesthetic sodium channel–blocking drug QX-314 preserved the anatomic integrity of injured motor axons of rats after compressive SCI, this was not translated into any measurable neurobehavioral benefit. A different local anesthetic, the sodium channel–blocking drug lidocaine, demonstrated a neural tissue–preserving effect and a positive effect on electrophysiologic parameters in a cat SCI model (19). In another experiment, Teng and Wrathall (38) administered the potent sodium channel–blocking neurotoxin tetrodotoxin to rats after contusive SCI. Compared with controls, the tetrodotoxin–treated rats demonstrated superior behavioral recovery at 8 weeks after injury as well as increased white matter preservation and reduced lesion size on postmortem histopathologic evaluation. However, the extreme toxicity of this compound precludes its translation to the clinic for use in human patients with SCI.

The neuroprotective properties of various sodium channel–blocking anticonvulsants, including riluzole and phenytoin, have also been evaluated in animal models of SCI. In a 2001 study from the Fehlings group, rats with clip-compression–induced SCI at C7-T1 received phenytoin, riluzole, CNS5546A (a novel sodium channel blocker), or a control vehicle via intraperitoneal injection. The animals were followed up to 6 weeks after injury, at which point the animals that received riluzole demonstrated improved functional outcomes relative to the other treatment groups, as measured by the Basso-Beattie-Bresnahan scale and inclined plane scores. Compatible with these findings, riluzole administration was also associated with significantly higher neuron counts in the brainstem observed using retrograde labeling, and a smaller area of tissue necrosis was seen on postmortem histologic analysis. These neuroprotective effects were replicated in a follow-up rat study from a Turkish laboratory, in which riluzole administration was associated with superior functional and histopathologic outcomes compared with phenytoin and a control vehicle. One potential explanation for the superior neuroprotective effects demonstrated by riluzole in vivo compared with phenytoin and other sodium channel–blocking anticonvulsants is the superior inhibitory effects on voltage-gated sodium channels that it has shown in vitro (33).

**RILUZOLE IN CLINICAL MEDICINE**

Riluzole was originally developed in the 1980s as an anticonvulsant drug tested
in various animal seizure models (24). Although it has never gained significant footing in the treatment of human epileptic patients, it has been applied to several different neurologic and psychiatric disease states, each of which has aberrant sodium metabolism or glutaminergic excitotoxicity as a presumed underlying pathologic mechanism.

ALS

In 1992, Rothstein et al. (28) documented impaired synaptic reuptake of glutamate in patients with ALS and hypothesized that this was contributing to the rapid degeneration of motor neurons seen in this disease. Previous preclinical studies demonstrated the potential of riluzole for reducing toxic extracellular glutamate accumulation, making this drug an attractive candidate for application to this “orphan” disease. In 1994, the results of the first phase III placebo-controlled randomized trial in ALS were published demonstrating a modest but significant survival benefit for participants treated with oral riluzole (6). Since this original publication, an additional three placebo-controlled randomized trials have been performed to confirm the efficacy of this drug (Table 2) (5, 20, 41). The results of these studies were summarized in a Cochrane review that included a meta-analysis of the available trial data (23). In this pooled analysis involving >1000 patients with ALS, the patients treated with riluzole at a dose of 100 mg/day experienced an increase in median tracheostomy-free survival of 2.8 months (15.5 months vs. 13.2 months). In addition, subtle beneficial effects were seen in the riluzole group with respect to limb and bulbar function. Although generally safe and well tolerated, the one potentially serious adverse event was that risk of serum alanine aminotransferase elevation (at least a 3-fold elevation) increased by a factor of 2.6 among treated patients. Although this side effect was observed in 16% of patients taking riluzole, it was witnessed only after several months of administration and was uniformly reversible with cessation of drug administration (23). Based on its demonstrated ability to increase survival with an acceptable safety profile, riluzole was the first drug approved by the Food and Drug Administration for the treatment of ALS, with recommendation to initiate long-term treatment at the time of diagnosis.

Other Clinical Uses

Apart from ALS, riluzole has been evaluated in several other progressive neurologic conditions over the last 20 years, including spinal muscle atrophy type 1, Huntington disease, and Parkinson plus disorder (progressive supranuclear palsy and multiple system atrophy) (7, 22, 39). Randomized controlled trials conducted to investigate the efficacy of riluzole in these conditions have failed to find a significant treatment-related effect. More recently, riluzole has been studied in the context of treatment-resistant depression. Several small open-label studies have shown riluzole to have significant antidepressant properties (42). Investigators at Yale University are currently enrolling patients with treatment-resistant depression in a randomized placebo-controlled trial to evaluate the drug’s efficacy in this context formally. To our knowledge, riluzole has not been formally evaluated in the clinical realm for traumatic brain injury or ischemic stroke, two other conditions in which ionic imbalance and glutamate toxicity contribute to the pathology.

**CLINICAL STUDY OF RILUZOLE FOR TREATMENT OF SCI**

Taking all factors together, riluzole represents a very promising compound for translation to the clinical realm for the treatment of human SCI for several reasons. First, as described earlier, it has documented preclinical efficacy rooted in a sound understanding of the biology of secondary injury events. Second, it has been shown to be clinically efficacious in ALS, a disease that has pathologic mechanisms that are analogous to the sodium and glutamate-mediated secondary injury events after SCI. Lastly, it has a well-defined safety profile in human patients with relatively few adverse effects known to be related to its administration.

Given these points, beginning in 2010 and completed in early 2012, an open-label phase I study was undertaken within the context of the North American Clinical Trials Network (NACTN) for SCI to investigate the safety and pharmacokinetic profile of riluzole in the treatment of traumatic SCI (15). A secondary objective of this study was to compare neurologic and functional outcomes from the riluzole-treated patients with outcomes from a prospective SCI registry matched for demographic and injury characteristics. During the 2-year study period, all patients presenting to one of the eight NACTN clinical centers were evaluated for eligibility. The study included adult patients with traumatic SCI with an American Spinal Injury Association impairment scale grade of A, B, or C and a neurologic level of injury between C4 and T2. Also, all patients had to be eligible to receive the

<table>
<thead>
<tr>
<th>Study</th>
<th>Description and Main Results</th>
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<tbody>
<tr>
<td>Bensimon et al., 1994 (6)</td>
<td>Tracheostomy-free survival at 1-year follow-up in 155 patients receiving either placebo or riluzole 100 mg/day: placebo group (58%), riluzole group (74%)</td>
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<td>Lacomblez et al., 1996 (20)</td>
<td>Dose-ranging study in 959 patients</td>
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<td>Tracheostomy-free survival at 18-month follow-up: placebo group (50.4%), riluzole 50 mg/day group (55.3%), riluzole 100 mg/day group (56.8%), and riluzole 200 mg/day (57.8%)</td>
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<td>100 mg/day dosage had best benefit/risk ratio</td>
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<tr>
<td>Yanagisawa et al., 1997 (41)</td>
<td>Japanese placebo-controlled trial</td>
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<td></td>
<td>No data on tracheostomy-free survival reported</td>
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<tr>
<td>Bensimon et al., 2002 (5)</td>
<td>Tracheostomy-free survival at 1-year follow-up in 168 elderly or advanced stage patients receiving either placebo or riluzole 100 mg/day: placebo group (63.4%), riluzole group (64.0%)</td>
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## Table 2. Summary of Completed Randomized Control Trials Evaluating Riluzole in the Context of Amyotrophic Lateral Sclerosis
study medication within 12 hours of the time of initial injury. This window was established as the most feasible time cutoff, balancing the desire to initiate neuroprotection as early as possible in the progression of secondary injury events with the practical realities of trauma care. Patients with a documented history of hepatic or renal impairment and patients with a preexisting mental or neurologic disorder that would preclude accurate evaluation were not enrolled. Lastly, because riluzole is available only in an oral formulation at the present time, patients who were not capable of receiving the drug orally or enterally via nasogastric tube were excluded.

Once enrolled, all patients received riluzole 50 mg orally or per nasogastric tube every 12 hours for 14 days after injury, with the duration of dosing prescribed based on the known length of sodium and glutamate-mediated secondary injury gleaned from preclinical experiments. Apart from riluzole, all patients were treated as per institutional standards at the discretion of the attending surgeon, with a push toward early surgical decompression wherever feasible. During the period of drug administration, regular serum drug levels were obtained, and detailed adverse event related information was maintained for each patient. The primary safety endpoint was 3 months; however, neurologic and functional outcomes were collected for 6 months in all cases. Although the final study analysis is still in progress, preliminary results appear sufficiently promising to justify proceeding with a larger trial to investigate formally the efficacy of riluzole in this patient population.

CONCLUSIONS AND FUTURE DIRECTIONS

The last several decades have been witness to dramatic improvements in understanding of the specific secondary injury mechanisms that collectively enlarge the area of cord injury and diminish prospects for neurologic recovery at follow-up. This enhanced understanding has permitted the investigation of targeted therapies for mitigating specific elements of this pathologic cascade. We now know that the continuous posttraumatic activation of neuronal voltage-gated sodium ion channels leads to increased rates of cell death through the development of cellular swelling, acidosis, and glutaminergic excitotoxicity. We also know that the anticonvulsant drug riluzole is a potent sodium channel blocker with documented preclinical efficacy in animal models of SCI. Although the clinical efficacy of this drug presently remains unknown, we look forward to embarking on a larger multicenter study in the coming months to address this question formally.

REFERENCES


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