Riluzole

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Introduction

This article includes discussion of riluzole and Rilutek. The foregoing terms may include synonyms, similar disorders, variations in usage, and abbreviations.

Historical note and terminology

Riluzole is a member of the benzothiazole class and is believed to be a glutamate antagonist. Several other glutamate antagonists (such as dextromethorphan and branched chain amino acids) have been tried previously for the treatment of amyotrophic lateral sclerosis, but without any success. Riluzole is the first drug to be approved for the treatment of amyotrophic lateral sclerosis; it received United States Food and Drug Administration approval in 1995 and was launched in several countries in 1996.

Pharmacology

Pharmacodynamics. The mode of action of riluzole is not known. The following pharmacologic properties may be related to its beneficial effect in amyotrophic lateral sclerosis:

- An inhibitory effect on glutamate release.
- Neuroprotective action of riluzole may be partly mediated by its increase of transporter-mediated glutamate uptake (Fumagalli et al 2008).
- Inactivation of voltage-dependent sodium channels.
- Ability to interfere with intracellular events that follow transmitter binding at excitatory amino acid receptors. Riluzole has been shown to be neuroprotective in experimental models of neuronal injury involving excitotoxic mechanisms. Transcranial magnetic stimulation has shown that riluzole reduces cortical excitability in patients with amyotrophic lateral sclerosis. This finding supports the view that attenuation of glutamate-related excitotoxicity is an important factor contributing to the beneficial effect. Riluzole has protective effects on dopamine neurons in vitro against neuronal injuries induced by impairment of cellular energy metabolism and oxidative stress. These results provide a basis for exploring the neuroprotective potential of riluzole in Parkinson disease.
- Riluzole increased the amount and activity of heat shock factor 1 to boost the expression of heat shock proteins and glutamate transporter 1, providing neuroprotection under stress (Liu et al 2011).
- Results of experimental studies on neurons and myotubes indicate that 1 of the mechanisms of riluzole’s therapeutic effect might be increasing the glucose transport rate in cells affected by amyotrophic lateral sclerosis (Daniel et al 2013).
- A longitudinal study of the effect of riluzole therapy on cortical hyperexcitability in patients with amyotrophic lateral sclerosis by using transcranial magnetic stimulation combined with peripheral nerve function excitability found transient modulation of cortical and axonal hyperexcitability as compared with healthy controls, which accounted for modest clinical effectiveness (Geevasinga et al 2016).

Pharmacokinetics. Important points are as follows:

- Riluzole is well absorbed following oral administration and has a bioavailability of 60%.
- Pharmacokinetics are linear over a dose range of 25 to 100 mg given every 12 hours.
• The mean elimination half-life is 12 hours after repeated doses.
• Riluzole is 96% bound to plasma proteins.
• Riluzole is metabolized to 6 major (and a number of minor) metabolites, some of which are pharmacologically active. All of the metabolites have not been identified. Metabolism is mostly hepatic and consists of cytochrome P450-dependent hydroxylation and glucuronidation.
• Excretion of riluzole is mainly renal as glucuronides.

**Delivery of riluzole to the brain.** Entry of riluzole into brain across the blood-brain barrier is restricted because it is a substrate of P-glycoprotein. A formulation of riluzole with lipid nanoparticles has been shown to improve delivery to the brain with greater efficacy than free riluzole in rats (Bondi et al 2010). Results of another animal experimental study indicate that nanoemulsion of riluzole for intranasal administration improves delivery to the brain and has the potential to reduce the dose of riluzole and avoid dose-related adverse events during treatment of amyotrophic lateral sclerosis (Parikh and Patel 2015).

**Clinical trials**

Main evidence for the approval of riluzole was based on a prospective, randomized, double-blind, placebo-controlled trial (Bensimon et al 1994). Riluzole appeared to slow the progression of amyotrophic lateral sclerosis and improve survival in patients with bulbar onset of the disease. Another double-blind, placebo-controlled, multicenter study was carried out to confirm these findings and to assess drug efficacy at different doses (Lacomblez et al 1996). The study confirmed that riluzole is well tolerated and lengthens survival of patients with amyotrophic lateral sclerosis. Efficacy and safety results suggest that a 100 mg dose of riluzole has the best benefit-to-risk ratio. Over an 18-month period, there was a 35% decreased risk of death with a 100 mg dose compared with placebo.

A review of riluzole in amyotrophic lateral sclerosis by the National Institute of Clinical Excellence in the United Kingdom concluded that riluzole was modestly effective and suggested that further studies were needed to gain further insights into its clinical effectiveness (Mitchell et al 2006).

The Cochrane Review of controlled clinical trials concluded that riluzole is reasonably safe and probably prolongs median survival of patients with amyotrophic lateral sclerosis by about 2 to 3 months (Miller et al 2012).

As of June 2016, 80 clinical trials of riluzole are listed on the United States government website: ClinicalTrials.gov. Most of these are for indications other than amyotrophic lateral sclerosis.

**Indications**

Riluzole is indicated for the treatment of amyotrophic lateral sclerosis.

**Off-label and investigational uses:**

• A randomized, double-blind, placebo-controlled trial has shown some benefit in patients with cerebellar ataxia (Romano et al 2015).

• Riluzole has been reported as useful for prevention of acute noise-induced hearing loss (Ruel et al 2005).

• Riluzole has been used to treat psychiatric conditions in children, particularly obsessive-compulsive disorder (Grant et al 2010).

• Autistic disorder (Wink et al 2011). A 10-week, randomized, double-blind, parallel-group, placebo-controlled trial showed that riluzole, when used as an adjunctive therapy to risperidone, improved irritability in children with autism, but it also significantly increased appetite and weight gain (Ghaleiha et al 2013).

• A phase I trial is evaluating the safety and pharmacokinetic profile of riluzole as a neuroprotective agent in patients with spinal cord injury (Chow et al 2012; Fehlings et al 2012).
• Riluzole increases glutamate uptake to increase synaptic glutamatergic activity in aged rats and protects them against age-related cognitive decline (Pereira et al 2014). Based on this, a clinical trial of riluzole is in progress for mild Alzheimer disease.

• A double-blind, placebo-controlled randomized trial of riluzole on patients with early cervical myelopathy did not show a significant change in the clinical outcome and diffuse tensor imaging (Rajasekaran et al 2016).

**Contraindications**

Riluzole is contraindicated in patients with hypersensitivity to riluzole or any of the tablet components.

**Goals and duration of treatment**

The aim of riluzole is to extend survival time of patients with amyotrophic lateral sclerosis. Riluzole is not a cure for amyotrophic lateral sclerosis, but the modest prolongation of survival that riluzole provides represents a first step forward in treating amyotrophic lateral sclerosis patients.

An outcome study of riluzole in amyotrophic lateral sclerosis concluded that riluzole therapy increased survival rates at 12 months by approximately 10% and prolonged survival by 6 months (Zoccolella et al 2007). The appropriate duration of riluzole treatment remains to be determined.

A 10-year observational study in Italy has evaluated the impact of riluzole and other therapeutic interventions on survival of patients with amyotrophic lateral sclerosis in a setting that resembles clinical practice more closely than randomized controlled trials (Georgoulopoulos et al 2013). Riluzole was shown to prolong life significantly longer than noninvasive ventilation and enteral nutrition.

**Dosing**

Dosing of riluzole is 50 mg every 12 hours.

**Special considerations**

Riluzole should be used with caution in patients with hepatic and renal insufficiency.

**Pediatric.** The safety and efficacy of riluzole in this age group have not been established.

**Geriatric.** Age-related decreases in liver and kidney function may cause a decrease in clearance of riluzole. Otherwise there are no differences in adverse effects between younger patients and those over the age of 65 years.

**Pregnancy.** Embryotoxicity has been observed in experimental animals given doses of riluzole equivalent to the maximum human therapeutic dose. No adequate and well-controlled studies have been conducted with pregnant women. Riluzole should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

**Anesthesia.** No special precautions.

**Interactions**

No clinical studies have been done to determine drug interactions, but a potential of interaction exists with hepatotoxic drugs and with those drugs that are highly bound to plasma proteins. Drugs that inhibit cytochrome P450 can increase the elimination of riluzole.

**Adverse effects**

Commonly observed adverse events in clinical trials with riluzole were asthenia, nausea, abdominal pain, dizziness, and liver enzyme elevation. Most of these are dose related. Riluzole treatment may be associated with mild blood pressure elevations. Riluzole may rarely cause neutropenia. Moderately severe acute pancreatitis has been associated with riluzole therapy (Ianiro et al 2014).

**Management.** Most of the adverse effects usually disappear after reduction of dose or discontinuation of therapy.
References cited


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**References especially recommended by the author or editor for general reading.

**Other pertinent drugs**

Glutamate antagonist

**Other topics to consider**

Amyotrophic lateral sclerosis
Clinical trials in neurology
Dementia associated with amyotrophic lateral sclerosis
Multiple sclerosis
Neuropharmacology
Neuroprotection for central nervous system disorders

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