Riluzole
A Review of its Pharmacodynamic and Pharmacokinetic Properties and Therapeutic Potential in Amyotrophic Lateral Sclerosis

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Riluzole, a benzothiazole, affects neurons by 3 mechanisms: by inhibiting excitatory amino acid release, inhibiting events following stimulation of excitatory amino acid receptors and stabilising the inactivated state of voltage-dependent sodium channels. It has demonstrated neuroprotective activity in vivo and in vitro.

Results from 2 randomised double-blind placebo-controlled trials in patients with amyotrophic lateral sclerosis (ALS; motor neuron disease) have demonstrated that riluzole can extend survival and/or time to tracheostomy. After 18 months, the relative risk of death or tracheostomy with riluzole 100 mg/day was reduced by 21%. Although riluzole slowed the rate of deterioration in muscle strength in the first trial, this was not confirmed in the second, larger trial. Riluzole had no effect on any other functional or secondary variable.

Gastrointestinal effects, anorexia, asthenia, circumoral paraesthesia and dizziness were reported more frequently with riluzole than placebo. Elevated alanine aminotransferase levels were observed in 10.6 versus 3.8% of patients treated with riluzole 100 mg/day versus placebo, leading to treatment withdrawal in 3.8 versus 2.1% of patients.

In conclusion, riluzole is the first drug that has been shown to have an effect on survival in patients with ALS. Although the effect of riluzole was modest, it has allowed some insight into the pathogenesis of ALS from which future gains may be made.

Amyotrophic lateral sclerosis (ALS; motor neuron disease) is characterised by progressive muscular weakness caused by degeneration of both upper and lower motor neurons. Sensory, autonomic and oculomotor neurons are almost completely unaffected. Patients usually die of respiratory failure within a median of 3.5 years.

Both sporadic and familial types of ALS occur. The familial form of the disease has been linked to mutations in the gene encoding Cu/Zn-dependent superoxide dismutase. A number of hypotheses to explain the pathogenesis of ALS have been proposed but the precise cause of this disorder is unknown.

Riluzole has 3 distinct effects on neurons. At micromolar concentrations, it inhibits both the release of excitatory amino acids and N-methyl-D-aspartate (NMDA) receptor-mediated events; these effects of riluzole may occur as a result of activation of a G protein-dependent process. Riluzole also stabilises the inactivated state of voltage-dependent sodium channels at low micromolar concentrations.

Riluzole has demonstrated neuroprotective effects in vitro and in vivo. In vitro, riluzole caused partial reversal of the effects of various neurotoxins in CNS cell culture or tissue slices.

In a transgenic mouse model of ALS, riluzole significantly extended survival by 11%, although it had no effect on disease onset. Riluzole has also demonstrated neuroprotective effects in animal models of ischaemia and other neurodegenerative diseases.

Riluzole has an average oral bioavailability of approximately 60%. Peak blood concentrations and the area under the concentration-time curve are reduced by about 45 and 20%, respectively, after a high fat meal. Steady-state plasma con-