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Review of the Use of the Glutamate Antagonist Riluzole in Psychiatric Disorders and a Description of Recent Use in Childhood Obsessive-Compulsive Disorder

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Abstract

The antiglutamatergic drug riluzole (Rilutek®) is presently being used off label in the treatment of psychiatric conditions in adult patients and, increasingly, in children. This article briefly reviews the pharmacology of this drug and its current investigative and clinical uses and adverse effects. It also reports on our experience to date in the study of the drug in children, with emphasis on adverse effects noted so far in these younger patients.

History

Riluzole was developed by Rhône-Poulenc Rorer in France as an antiepileptic agent. However, it has no current United States Food and Drug Administration (FDA) indication except for its use in amyotrophic lateral sclerosis (ALS) (Rilutek package insert). In ALS, a motor neuron disease that results in nerve cell degeneration in the central nervous system (CNS) and peripheral nervous system, riluzole has been reported to extend the time before the need for respirator use by some months (Lacomblez et al. 1996; Miller et al. 2003). It is not clear that it prolongs life in ALS (Logroscino and Zoccolella 2007).

Mechanism

The mechanism of action of riluzole in the nervous system is complex. A considerable number of actions have been demonstrated *in vitro*, but some of these may have little relevance *in vivo*, where much lower concentrations of riluzole are achieved. Pittenger and colleagues have recently reviewed the subject very capably (Pittenger et al. 2008b).

Riluzole inhibits the release of glutamate at the presynaptic nerve cell terminus, most likely by blockade of voltage-gated sodium channels, and this effect may be achieved at low riluzole concentrations (demonstrated most recently by Urbani and Belluzzi 2000). It also likely reduces glutamate neurotransmitter vesicle fusion with the presynaptic cell membrane, either directly by opening voltage-gated calcium channels (Wang et al. 2004) or indirectly by altering G-protein–mediated signaling (Huang et al. 1997). Riluzole's effects on potassium channels have also been measured, but possibly not at clinically meaningful riluzole concentrations (Ahn et al. 2005; Mathie and Veale 2007).

Downstream effects of riluzole have been noted as well, but clinical significance remains unclear. These effects are stimulation of growth factor synthesis, including brain-derived neurotrophic factor (Fumagalli et al. 2006), and promotion of neuritogenesis, neurite branching, and neurite outgrowth (Shortland et al. 2006).

Riluzole has not been found to interact with any glutamate receptors at clinically meaningful concentrations (Habibi-Asl et al. 2009). However, enhancement of the hippocampal α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) glutamate receptor (GluR1, GluR2) subunit expression (Du et al. 2006) has been noted. And at high concentrations, there has been measured antagonism of AMPA and *N*-methyl-D-aspartate (NMDA) receptors (Pittenger et al. 2008b). Riluzole increases glial glutamate reuptake, possibly at the low levels found only extrasynaptically (Frizzo et al. 2004; Fumagalli et al. 2008).

In a recent study, riluzole (4 mg/kg, a reasonable dose when used in humans) attenuated the behavioral effects of chronic unpredictable stress, a rodent model of depression (Banasr et al. 2010). In the same study, the investigators demonstrated that metabolic and mRNA expression effects of stress were also attenuated by riluzole. These results are consistent with the evidence for the riluzole-enhanced reuptake of glutamate by glial cells. In addition, riluzole (10 μM) has been shown to exhibit a neuroprotective effect on rat glial cells to which a toxic level of glutamate (100 μM) was added in culture (Dagci et al. 2007).

There have been reports of riluzole effects on other neurotransmitters, but there has been little replication of these findings so far.

Pharmacokinetics

In adults, riluzole taken orally without food is about 60% absorbed. A fatty meal delays or reduces absorption. Peak serum level in healthy volunteers is achieved after about 1–1.5 hours and trough levels are reached at about 12 hours. Riluzole is 96% bound to plasma proteins. Steady-state levels at stable dose are achieved after about 5 days. Plasma elimination half-life ranges from about

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9 to 14 hours, independently of dose. Steady-state trough serum levels are significantly higher with larger doses, but values under the serum concentration–time curve do not change (Le Liboux et al. 1997; Le Liboux et al. 1999). The dose generally used in ALS is 50 mg of riluzole every 12 hours. This dose seems to provide the best benefit-to-risk ratio (Lacomblez et al. 1996).

The primary metabolic pathway is hydroxylation (to *N*-hydroxyriluzole) by the cytochrome P450 enzyme 1A2, followed by glucuronidation (Wokke 1996). There also seems to be some direct glucuronidation (Sanderink et al. 1997; van Kan et al. 2008). Extrahepatic 1A1 may result in other metabolites. Phenotypic variation of 1A2 enzyme activity and occupation of that enzyme by other substrates are theoretical considerations in serum level effects (Sachse et al. 1999). But 1A2 activity has been shown to account for only 37% of the variability in riluzole serum level (van Kan et al. 2004), and neither 1A1 nor 1A2 genetic variability is likely to affect serum riluzole levels (Ajroud-Driss et al. 2007).

It has been shown that interindividual variation of riluzole serum level is much larger (by a factor of 50 times peak levels) than intraindividual variation (Bruno et al. 1997; Groeneveld et al. 2001). However, neither phenotypic variation in glucuronidation (UDT1A1*28 variability) (van Kan et al. 2008) nor P450 polymorphisms account for mean riluzole serum levels, at least in ALS patients.

Less than 1% of the drug is excreted unchanged in urine, and less than 10% of the metabolized drug in feces (Wokke 1996). More than 90% of the drug is excreted in urine as metabolites, mainly as various glucuronides. Clearance of the drug is independent of dosage, but males and smokers (probably because of 1A2 induction) clear the drug faster than women and nonsmokers (Bruno et al. 1997).

Riluzole is known to cross the blood–brain barrier easily (Wokke 1996). But in a cell culture study, the drug was shown to increase the activity of breast cancer resistance protein, an efflux pump that prevents riluzole (and other chemicals) from crossing the blood–brain barrier. Therefore, riluzole induces a self-barrier to its own brain activity (Milane et al. 2009). Minocycline, a tetracycline antibiotic, on the other hand, inhibits P-glycoprotein, another efflux pump, so that when administered with riluzole it results in higher riluzole brain levels in an animal model (Milane et al. 2007).

Adverse Effects

The one clinical study that attempted to correlate adverse effects and benefits with serum levels found that diarrhea was more common at higher doses, but fasciculations were less common (possibly implying a neuromuscular benefit) (Groeneveld et al. 2003). No relationship was found between riluzole serum levels and survival in one study (Groeneveld et al. 2008).

The adverse effects of the drug are generally mild in physically healthy adults (Le Liboux et al. 1997). Long-term effects are unknown, because the majority of use has been in patients with ALS, generally a fatal condition. But, in one report, riluzole was found to be well tolerated for periods up to 7 years (Lacomblez et al. 2002).

The most common adverse effect reported is elevation of transaminases, especially alanine aminotransferase (ALT), but rarely to more than three times upper limits of laboratory normals (Miller et al. 2003). Acute hepatitis has been reported rarely at usual doses of riluzole, in one case recurring with rechallenge (Remy et al. 1999).

Other adverse effects are reported less frequently. Two case reports of leukopenia (North et al. 2000; Weber and Bitterman 2004) and two cases of methemoglobinemia have been reported (at least in overdose) (Viallon et al. 2000; Woolf et al. 2004). There have been at least two reports of hypersensitivity pneumonitis (Cassiman et al. 2003; Borderias-Clau et al. 2006) and one of a more generalized multiorgan autoimmune phenomenon (Sorenson 2006). There has been a single case report of normoglycemic glycosuria, polydipsia and polyuria, and hypercalciuria and hyperuricuria, suggesting defect of tubular function (Poloni et al. 1999). And in an *in vitro* study, riluzole, in a local concentration of 250 μM and above, was toxic to mouse renal cells (Chen et al. 2006). There have been 12 reported cases of possible drug-induced pancreatitis in adults with ALS taking riluzole (Drory et al. 1999; Rodrigo et al. 2001). At the National Institute of Mental Health (NIMH), in the Pediatrics and Developmental Neuroscience (PDN) Branch, we have seen two additional cases of pancreatitis, probably related to riluzole, in young subjects in our ongoing riluzole trial in pediatric obsessive-compulsive disorder (OCD) (see below.)

There have been no deaths reported in the world literature, even after deliberate overdose (in which case supportive care was followed by recovery) (Viallon et al. 2000; Bodner et al. 2001).

Clinical Uses in Psychiatry

Because of its antiglutamatergic effect and its relative safe profile, riluzole has been used in a number of trials for psychiatric conditions in which glutamate excess has been proposed as part of the pathologic mechanism. There have been seven open-label trials of riluzole (three of them using riluzole as monotherapy) in adult subjects: Three in major depressive disorder (MDD) (Zarate et al. 2004; Sanacora et al. 2007; Mathew et al. 2010), one in bipolar depression (Zarate et al. 2005), one in generalized anxiety disorder (GAD) (Mathew et al. 2005), and two in the treatment of OCD (Coric et al. 2005; Pittenger et al. 2008a).

There has been only a single reported study in children, a small open-label trial in childhood OCD in which riluzole was added to other medications (Grant et al. 2007). There has been a recent review of these studies (Pittenger et al. 2008b). See Table 1 for details of these studies, including outcomes. The only other previous use of riluzole in any childhood condition was a small open-label trial in spinal muscular atrophy, a neuromuscular condition of infancy, usually fatal before age 2 years. In that trial, riluzole was given at a dose by weight that would be equivalent to 200 mg daily in an adult. Three of the seven children who received active drug riluzole were alive at the end of the study, although this was not a statistically significant outcome (Russman et al. 2003). No follow up has been published, and no similar study has been reported.]

There have been a number of case reports:

- Riluzole augmentation for OCD and MDD (Coric et al. 2003).
- Riluzole augmentation for bipolar depression (Singh et al. 2004).
- Riluzole augmentation for MDD (Sanacora et al. 2007).
- Riluzole for borderline personality disorder with self-injurious behavior (Pittenger et al. 2005).
- Riluzole for disordered eating and skin-picking (Sasso et al. 2006).
- Riluzole for trichotillomania (Coric et al. 2007).

Current OCD Trial at NIMH/PDN

A preliminary report on the ongoing trial at the NIMH is presented here in the context of riluzole use and adverse effects in childhood. In the open-label trial described above (Grant et al.

Table 1. Clinical Trials in Psychiatry

Author	*Subjects*	*Study design*	*Adverse Effects*	*Key Findings*
Zarate et al. (2004)	19 adults with depression 13 completed trial	Open-label; One-week drug-free period followed by riluzole alone, 100–200 mg/day (avg 169 mg) for 6 weeks	One subject who had three times elevation of liver function tests which normalized after discontinuation of drug.	46% of study completers had $\geq$50% decrease in MADRS scores at week 6. Improvements observed on HAM-D and HAM-A.
Coric et al. (2005)	13 adults with OCD	Open-label; 50 mg of riluzole added to current treatment	No major adverse effects.	7 had >35% reduction in CY-BOCS scores; 5 had >35% reduction in CY-BOCS and a final Y-BOCS of 16 or less.
		Initially treated for 6 weeks then extended to 12 weeks.	One patient's initially elevated alanine aminotransferases (ALT) declined with study progression.	HAM-D and HAM-A scores also improved significantly over time, with mean scores dropping from 30 ($\pm$ 13.7) at baseline to 19.7 ($\pm$ 6.0) and from 18.2 ($\pm$ 6.2) to 12 ($\pm$ 2.5), respectively.
Mathew et al. (2005)	18 adults with GAD 15 completed trial	Open-label; 100 mg riluzole/day for 8 weeks after 2-week drug washout.	No major adverse effects	Median response time was 2.5 weeks. 12 subjects had $\geq$50% decrease on HAM-A scores at study completion. Mean scores dropped from 20 ($\pm$ 3.4) at baseline to 7.5 ($\pm$ 5.3) at week 8. 8 patients were in remission at study completion (HAM-A score of $\leq$7).
Zarate et al. (2005)	14 adults with depression and bipolar disorder. 8 completed trial	Open-label; Supplementation of 50–200 mg daily riluzole if still depressed (MADRS score $\geq$20) after 4-week treatment with lithium. Riluzole supplemented 8 weeks thereafter.	2 subjects had elevations in liver function tests which normalized after discontinuation of the drug.	Significant improvements on the MADRS, with 7 subjects entering remission (MADRS score of $\leq$12) at the end of 8-week trial. No switch to mania or hypomania.
Grant et al. (2007)	6 children with OCD (ages 8–17, mean 14.4 years)	Open-label; 100–200 mg riluzole daily added to previously prescribed medications for 12 weeks (2 subjects not on any other medication at baseline).	No major adverse effects	4 out of 6 subjects were Much- or Very Much-Improved on the CGI scale. 39% reduction on CY-BOCS for the group as a whole. 1 subject improved later
Sanacora et al. (2007)	15 adults with MDD 10 completed trial	Open-label; 50 mg riluzole added for 6 weeks to ongoing medication regimen, followed by optional 6-week continuation phase.	No major adverse effects	HAM-D and HAM-A scores decreased by 36% and 31%, respectively, from baseline by the end of week 6. Response time was as early as 1 week and remained significant for entire study phase.

(*continued*)

Table 1. (Continued)

Author	*Subjects*	*Study design*	*Adverse Effects*	*Key Findings*
Pittenger et al. (2008)	13 adults with OCD (9 also had concomitant MDD.	Open-label; 50 mg twice a day (bid) up to 100 mg bid; other medicines adjusted *ad lib.*	No major adverse effects	6 of 13 subjects had $\geq$35% reduction in Y-BOCS in 12 weeks. 2 others improved later. $\geq$31% drop in average scores on HAM-A, $\geq$28% drop in average scores on HAM-D.
Mathew et al. (2009)	26 medication-free adults with MDD.	Double-blind; Ketamine (IV) administered 0.5 mg/kg over 40 min after pre-treatment two hours prior with 300 mg lamotrigine or placebo. Among those whose depression failed to improve at 72 hours participated in a 32-day double-blind trial of riluzole 100–200 mg/day.	No major adverse effects	65% responded to treatment, with $\geq$50% reduction on MADRS 24 hours after ketamine. Lamotrigine did not attenuate the side effects nor enhance antidepressive effects. No significant difference in time-to-relapse between riluzole and placebo. Thus, early termination of study.

Abbreviations: bid = twice a day; CGI = Clinical Global Impressions; CY-BOCS = Children's Yale-Brown Obsessive-Compulsive Scale; GAD = generalized anxiety disorder; HAM-A = Hamilton Anxiety Scale; HAM-D = Hamilton Depression Scale; MDD = major depressive disorder; MADRS = Montgomery-Åsberg Depression Rating Scale; OCD = obsessive-compulsive disorder; Y-BOCS = Yale-Brown Obsessive-Compulsive Scale.

2007) in which riluzole was used for childhood OCD, 4 of 6 young people were Much- or Very Much-Improved on the Clinical Global Impressions–Improvement Scale (CGI-I) and were 39% improved overall on the Children's Yale-Brown Obsessive-Compulsive Scale (CY-BOCS). On the basis of that experience, the Institutional Review Board at the NIMH of the National Institutes of Health (NIH) permitted the PDN Branch to proceed with a double-blind, placebo-controlled (DBPC) trial of the drug, in which riluzole or placebo was added to currently inadequately effective pharmacotherapy in youths, ages 7–17 years. All subjects had to have moderate to severe OCD. Half of the enrolled subjects may also have a diagnosis on the autism spectrum (as well as OCD).

All young subjects had to meet criteria for OCD. But in some cases, when the youth also had a disorder on the autism spectrum, the obsessions seemed more like the preoccupying interests and repetitive behaviors common to an autism diagnosis. Nevertheless, the youths with an autism spectrum disorder had to meet the research team's criteria for OCD as well as the CY-BOCS score requirement. Nonautistic youths had typical OCD symptoms. A thorough description of the subjects and the study results will be reported promptly when the study is complete.

In this trial, the current drug regimen of the young subjects was continued unchanged for at least 6 weeks prior to starting study drug, and remained unchanged during the 12 weeks of the double-blind trial. Some drugs (e.g., fluoxetine, clomipramine) were not permitted because of concern about drug–drug interaction with riluzole. On the basis of our experience to date, such an interaction may be more than only theoretical (see below). These drugs must be tapered and stopped at least 6 weeks prior if the subject and family are motivated to enter the study. There are only very few exclusionary diagnostic conditions: Serious liver or kidney disease or other significant medical condition, psychotic disorders, suicidality or dangerous aggressiveness, and severe eating disorder symptoms (with consequent medical instability).

After 12 weeks of the DBPC trial, subjects may elect to take open-label riluzole. So far, every child, with parental concurrence, has elected to take the open-label drug. Children are followed at the NIH for 1 year from the time of enrollment in the study. At every study visit, clinical laboratory tests are obtained to look for adverse effects: Complete blood cell counts, serum chemistries including measures of liver and kidney function, amylase and lipase as harbingers of pancreatic inflammation, and urinalysis including microscopic examination. At baseline, and periodically thereafter, although not at every visit, electroencephalograms (EEG) and electrocardiograms (ECG) are also obtained. In addition, at every phlebotomy, a serum sample is stored at -80°C. Almost all subjects continued to take riluzole for the 1-year duration of the study, and a number of young subjects continue to take riluzole to the present time. Some have discontinued all other psychiatric medications.

Experience So Far

Adverse effects are discussed below because they occurred during both phases of the study—DBPC and open-label. The young subjects in this study easily tolerated the doses usually prescribed for adults, 50 mg every 12 hours. Because double-blind data have not been analyzed, we do not know if any symptom has been reported with more frequency with riluzole than with placebo. However, in the double-blind phase, no symptom has been reported with any consistent frequency nor caused any subject to wish to discontinue drug.

The single exception during the double-blind phase was 1 adolescent who developed abdominal pain due to pancreatitis about 6 weeks after starting the study drug. On routine measurement, this

male's serum amylase was normal only 10 days prior to onset of symptoms. He was hospitalized and had a full recovery. The study blind was broken in his case, and he was found to be taking the active drug. Riluzole was discontinued at once and has not been resumed. It should be noted that he was taking three other drugs at the time (citalopram 40 mg daily, clomipramine 25 mg at bedtime, and quetiapine 600 mg at bedtime), all of which were reportedly continued after his recovery.

A second child developed pancreatitis just after completing the 1-year protocol and while still taking open-label riluzole. She would have taken the active drug for at least 9 months at that point. It may be relevant that this female had also resumed taking fluvoxamine at the time pancreatitis symptoms appeared after stopping it during the NIMH trial. Fluvoxamine also occupies the 1A2 enzyme, and her serum riluzole levels were consistently higher than those of any other of our subjects measured so far (see below). She stopped riluzole when pancreatitis developed and has also had a complete recovery from that adverse effect.

No other symptom has been reported with any meaningful frequency in the open-label phase. One child discontinued open-label riluzole because of the new onset of a tic.

All other adverse effects have been only laboratory abnormalities. As with adult subjects, elevation of transaminases has been the most frequent finding. In only one case has riluzole been stopped for this reason. In that case, an adolescent male continued to have transaminases rise then fall when drug was stopped, only to rise again on rechallenge during the open-label phase. In his case, there was known steatosis of liver even prior to starting the study drug, and enrollment in the study was allowed only after consultation with pediatric gastroenterology and with full consent of both parents. (The boy has autism and could not understand nor assent to his treatment.)

In a few other cases, the double-blind study drug was discontinued because of transaminase elevations, but only because the study team has a low threshold for this adverse effect. In each of those cases, open-label drug has been offered and has been taken and well tolerated.

Discussion

It is apparent that our experience with the use of the drug riluzole has been very much like the experience of clinicians treating adults with ALS. In this young study population, laboratory and symptomatic adverse effects are complicated by the fact that subjects are taking concomitant medications, often multiple medications. The study has deliberately recruited young people who have failed standard-of-care treatments and who remain quite impaired by their OCD. But the drug has largely been well tolerated. Two subjects developed pancreatitis, but they were also taking concomitant medications. One subject with fatty infiltration of liver preceding study enrollment stopped the open-label riluzole because of transaminase elevations.

We have begun measuring riluzole serum levels in samples obtained during the open-label phase of this study. At conclusion of study, we will measure riluzole levels from the double-blind phase as well. These measurements and their relevance to the use of the drug and to adverse effects will be the subjects of a subsequent report.

We have so far enrolled a total of 46 subjects in the DBPC riluzole trial, and we intend to enroll a total of at least 60 young people. The outcome data will be reported promptly after study is complete.

Conclusions

Riluzole seems to be well tolerated in adults and in young people at the doses used in treating ALS in adults. The cases of pancreatitis are quite concerning; pancreatitis has been reported rarely in adults taking the drug. But pancreatitis is an uncommon adverse effect associated with many drugs that have generally good safety profiles (Andersen et al. 2001). If riluzole proves effective for psychiatric conditions, including conditions in childhood, then it may be used as monotherapy in the future with an acceptable safety profile.

Disclosures

The authors have no corporate or commercial relationships and no conflicts of interest to disclose.

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