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Riluzole Serum Concentration in Pediatric Patients Treated for Obsessive Compulsive Disorder

Paul Grant, MD, Cristan Farmer, PhD, Jane Song, MD, Timothy Kish, BA, and Susan Swedo, MD

Section on Behavioral Pediatrics, National Institute of Mental Health, Bethesda, MD, USA

Abstract

Purpose/Background—The goal of this study was to determine whether pediatric serum concentration of riluzole is similar to that observed in adults, and to determine whether riluzole serum concentration is associated with adverse effects or efficacy in children and adolescents with treatment-refractory obsessive-compulsive disorder.

Methods/Procedures—Data were drawn from previously published studies: one open-label trial and one randomized controlled trial with an open-label extension phase. Serum was drawn at 24, 36, and 52 weeks in 37 patients who were taking approximately 100 mg riluzole daily (mean dose at 24 weeks, 99 ± 28 mg).

Findings/Results—Across all samples, serum riluzole concentration ranged from 7 ng/mL to 963 ng/mL. At week 24 ($n=37$), the median concentration was 76 ng/mL (IQR=53–172). Concentration was relatively stable within-patient. One subject, who had the highest serum concentration levels during the study, developed pancreatitis after exiting the study. The patient had recently added fluvoxamine to the riluzole regimen. Controlling for concomitant fluvoxamine (in six participants) and time-of-draw, serum riluzole concentration was not associated with obsessive compulsive disorder symptom severity; nor was it associated with side effect profile.

Implications/Conclusions—The dose of riluzole used in these pediatric subjects appears to have achieved serum concentration levels similar to those observed in adults. However, as previously reported in adults, the serum concentration had no discernable relationship to efficacy or adverse effects. [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT00251303): NCT00251303.

Keywords

riluzole; obsessive compulsive disorder; serum concentration

INTRODUCTION

Riluzole is a glutamatergic modulator that is used, off-label, to treat some psychiatric conditions in adults¹. The adverse effects of riluzole are generally mild in physically healthy subjects². The most commonly reported adverse effect is elevation of transaminases,

Corresponding Author: Paul Grant, paul.grant@nih.gov, 10 Center Drive, Bethesda MD, 20892.

DISCLOSURES

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especially alanine aminotransferase, but rarely to more than three times upper limits of laboratory normal³. The one clinical study that attempted to correlate adverse effects and benefits with riluzole serum levels found that diarrhea was more common at higher doses in adults⁴. No relationship was found between riluzole serum levels and survival of adults treated for amyotrophic lateral sclerosis (ALS) in another study⁵.

Peak serum levels in healthy adult volunteers is achieved after about sixty-to-ninety minutes, and trough levels at about twelve hours. Inter-individual variability of riluzole serum concentration is far greater than within-individual variability^{2,6}. In one study of adults with ALS, the serum riluzole levels associated with a 50 mg twice-daily dose had a median trough value of 54 (range 20–343) and a median peak value of 183 (44–1,552) ng/ml⁵. However, within-subject variability is high; in another study of ALS patients, visit-to-visit variability (28%) was confirmed to be lower than between-subject variability⁷.

Plasma concentration may vary across patient population; a study of adults with acute spinal cord injury documented lower peak plasma concentrations than observed in ALS patients at the same dose⁸. In that study, free riluzole after ultrafiltration was measured in a subset and did not account for the differences noted in total drug⁹. Of particular relevance to the present report, a study of 14 young patients (ages 6–20 years) with spinal muscular atrophy documented maximum concentrations *higher* than observed in both healthy subjects and ALS patients; the authors speculate that the pathophysiology was responsible for the altered pharmacokinetics, rather than other variables such as age or weight¹⁰.

Intra-individual variability may be partially explained by metabolic activity. *In vitro* data suggest that riluzole is predominantly metabolized by CYP1A2 human hepatic microsomes to the N-hydroxy conjugate, and glucuronidation appears to be a “relatively minor metabolic route”¹¹. However, among ALS patients, cytochrome P450 1A1 and 1A2 polymorphisms were *not* demonstrated to account for mean riluzole serum level differences¹². Another study of ALS patients used serum caffeine metabolism as a probe of CYP1A2 activity; while the activity was significantly correlated with riluzole clearance, it only explained 37% of the variability¹³. The authors speculated that the large inter-individual variation is possibly attributable to glucuronidation and extra-hepatic CYP1A2 activity¹³. Following on this, glucuronide formation *in vivo* was confirmed in serum from ALS patients, and the metabolite concentration was positively associated with drug levels¹⁴. In the same publication, UGT1A1*28 genotype was *not* associated with peak or trough concentrations in a second larger group of ALS patients, leading the authors to conclude that glucuronidation is not a major contributor to inter-individual pharmacokinetic variability¹⁴.

Given the interest in glutamate as a therapeutic target in obsessive-compulsive disorder (OCD)^{15,16}, we conducted an open-label trial of riluzole in six children with OCD¹⁷. In that study, riluzole was well-tolerated, and we hypothesized that a longer duration of treatment would result in symptom improvement. Thus, we completed a 12-week, randomized, placebo-controlled, double-blind trial (RCT) of riluzole in children and adolescents with treatment-refractory OCD and, in some cases, with co-occurring autism spectrum disorder¹⁸. To make study participation attractive, the RCT study design included open-label administration of riluzole from 12 weeks to 52 weeks. During the double-blind portion of

that study, all participants experienced improvements in OCD symptoms, but there was no advantage of riluzole compared to placebo. Interpretation of the results was moderated by the fact that the children were treatment-refractory, and the majority received concomitant medications. Specifically, 71% of the sample was taking a selective serotonin reuptake inhibitor and at least one additional psychotropic medication. Further, given the documented variability in adults of riluzole serum concentration, it was considered possible that the study dose (100mg/day) was not adequate for some participants.

In this report, we combine data from the open-label pilot study¹⁷ and the open-label portion of the RCT¹⁸ to address the question of whether riluzole serum concentration is associated with clinical response or adverse effect profile in our young subjects.

METHODS

Participants

Data were drawn from two studies completed in the Pediatrics and Developmental Neuroscience Branch of the National Institute of Mental Health of the National Institutes of Health. Both studies were approved by the National Institute of Mental Health Institutional Review Board, and consent/assent was obtained for all participants. The full details of both reports are found elsewhere^{17,18}.

Participants in the current investigation were all those who received open-label administration of riluzole, who attended follow-up visits at 24 weeks, 36 weeks, and/or 52 weeks post-baseline, and whose serum sample was tested on at least one of those occasions. The final sample, from the 66 eligible participants in the original studies, comprised 37 individuals (five from the pilot study and 32 from the RCT); 27 (73%) were male, and all were Caucasian. These participants ranged in age from 8.8 to 18.4 years ($M \pm SD = 14.6 \pm 2.7$) at the Week 24 visit. Body mass index (BMI) at the final study visit ranged from 15.1 to 37.2 ($M \pm SD = 25.5 \pm 5.1$).

Procedures

During the open label portion of the RCT study (starting at week 12 post-baseline), most participants were prescribed 50 mg of riluzole every 12 hours. Doses had been titrated during the transition to open label on a fixed schedule, with a target dose of 100 mg/day, barring any adverse effects. The open-label protocol did allow for dose adjustment, and the pilot study was partially dedicated to dose-finding, so the mean daily dose for all participants varied across visit (week 24, $M \pm SD = 99 \pm 28$; week 36, 108 ± 28 ; week 52, 120 ± 34). However, across all study visits, the median daily dose was 100 mg. Exact doses for each subject are recorded in Supplementary Table 1. Daily diaries were to be kept of doses and physical symptoms. For adverse effect monitoring, clinical laboratory tests were obtained at all study visits. Exact timing of the morning dose was not available, so a time of 8:00 AM was used to approximate the amount of time passed between the morning dose and venipuncture, the exact time of which was recorded. This value is referred to herein as *time-to-draw* (in hours). The serum samples were stored at -80°C until they were batched and sent for analysis.

Frontage Laboratories, Inc. (700 Pennsylvania Dr., Exton, PA 19341) measured the total riluzole in these serum samples, blind to subject and to riluzole administration. Because there were no published methods for the measurement of total riluzole in biological samples, the laboratory used a liquid chromatography/tandem mass spectrometry method developed specifically for this study. The method was developed and validated for the determination of riluzole in human serum using 2-amino-6-bromobenzothiazole as the internal standard (IS). The high performance liquid chromatography column (HPLC) was Agela Venusil XBP C18 100A, 2.1 × 50 mm, 5 micron. Mobile Phase A was 0.1% HCOOH in MeOH/H₂O (2/98, V/V). Mobile Phase B was 0.1% HCOOH in MeOH. The retention time of riluzole was 1.6 minutes, and the retention time of the IS was 1.3 minutes. Sciex API 4000 with Interface TIS was used to monitor riluzole and IS in positive ionization mode. The transitions were m/z 235.1 → 138.1 for riluzole, and m/z 231.0 → 150.0 for IS. Human serum samples of 100 μ L were used for analysis. The serum samples with 20 μ L of IS (1 μ g/mL of ABBT) were extracted with MTBE. The organic phase was dried down and reconstituted with 0.1% Formic Acid in MeOH/H₂O (50/50, V/V), and 10 μ L of the final solution was injected onto the HPLC column.

Behavioral data were obtained at each study visit; in this study, the Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS) total score was the primary outcome¹⁹.

Analysis

A mixed model with a random effect of subject, to account for repeated observations, was used for all analyses where serum concentration was the dependent variable. The covariance structure was compound symmetry. A generalized linear mixed model with random intercept was used to evaluate the relationship between concentration and (binary) side effects. Serum concentration was natural log-transformed to accommodate distributional assumptions. Alpha was set to .05. All analyses were performed in SAS 9.3²⁰.

RESULTS

Thirty-seven participants contributed serum data at the 24-week visit, 30 (81%) had additional data at the 36-week visit, and a further 22 (59%) had 52-week data. Across the 89 samples, 28% were collected before 12:00 PM, and 70% between 12:00 PM and 4:00 PM. Across all samples, serum riluzole concentration ranged from 7 ng/mL to 963 ng/mL. At week 24 ($n=37$), the median concentration was 76 ng/mL (interquartile range, IQR=53–172). Concentrations were similar at week 36 ($n=30$, median=81, IQR=44–128) and week 52 ($n=22$, median=95, IQR=59–192). Dose was not associated with serum concentration [$F(1,51)=0.33$, $p=.57$], but it was still retained in the remainder of the analyses as a covariate. See Figure 1 for serum riluzole levels by patient, over time. The full dataset, including time-of-draw.

Six participants (16%) received fluvoxamine, a CYP1A2 inhibitor, during the open-label study. Controlling for riluzole dose, concomitant fluvoxamine use was significantly associated with higher riluzole concentration; the least squares mean estimate for individuals not taking fluvoxamine was 79 ng/mL, compared to 164 ng/mL in those taking fluvoxamine [$F(1,50)=4.68$, $p=.035$].

Riluzole concentration was not related to BMI [$F(1,51)=0.36$, $p=.55$]. Pharmacokinetic studies⁷ have documented an exponential decline of riluzole over time, but in this study, time of blood draw was linearly and significantly related to riluzole concentration, such that each additional hour was associated with a decrease of approximately 1 ng/mL ($SE=1$) [$F(1,50)=4.81$, $p=.03$]. Thus, both concomitant fluvoxamine and time-of-draw were entered with riluzole dose as a covariate in the final analysis. Controlling for time-of-draw [$F(1,47)=0.85$, $p=.36$] and fluvoxamine [$F(1,47)=0.39$, $p=.54$], natural log-transformed serum riluzole concentration was not associated with CY-BOCS score [$F(1,47)=1.36$, $p=.25$] (see Figure 2).

One female child developed pancreatitis after finishing the study and while still taking riluzole. Fluvoxamine, which is an inhibitor of the 1A2 enzyme, had recently been added to her regimen because of continuing symptoms. There had also been a seemingly mild abdominal injury prior to onset of pancreatitis. Riluzole was stopped, and she fully recovered. Although the pancreatitis developed after participation in the study ended (but before serum data were analyzed), we note that this child's serum riluzole levels were the highest observed in the study (week 24, 963 ng/mL; week 36, 943 ng/mL; no data at week 52).

Elevated transaminases were the only frequent laboratory finding (in 10 patients at 12 visits). Controlling for dose, serum concentration did not predict the presence of elevated transaminases [$F(1,50)=0.03$, $p=.85$]. No other side effect occurred with enough frequency to determine a relationship with serum concentration.

DISCUSSION

In this report, we utilized data from two open-label studies of riluzole for the treatment of OCD in pediatric patients to investigate the variability of riluzole serum concentration and its association, if any, with symptom severity and adverse effects. There were several objectives in measuring serum riluzole levels in this sample. First, we wished to know if serum levels in younger subjects were comparable to those achieved in adults taking similar doses. Serum concentration among the children and adolescents in this study was similar in range and variability to what is reported in the adult data. Second, we wanted to know if adverse effects were associated with serum levels, and we found no evidence to support this connection. The interpretation of the adverse event data is complicated by the fact that many patients were taking concomitant medications during the open label administration of riluzole. This was not surprising, given that our studies deliberately recruited young people who had failed standard-of-care treatments and who remained quite impaired by their OCD. As one would predict, concomitant fluvoxamine, a CYP1A2 inhibitor, was associated with increased riluzole serum levels. The practical meaning of this is unclear, since ideal (or toxic) riluzole level is unknown. It is worthy of note that the child who developed pancreatitis during the open label phase had the highest riluzole serum levels. However, we were not able to determine if this was coincidence or causally related, as she had begun taking fluvoxamine prior to development of the pancreatitis. Third and finally, we sought to determine whether serum level of riluzole was associated with clinical effect. Based on these open label data, serum level of riluzole does not appear to have any bearing on severity of

OCD symptoms. Thus, although the serum concentration was variable across participants, it did not appear to relate to symptom severity.

This study had several limitations. The sample size is relatively small. However, we note that there are no other available reports of riluzole use in pediatric patients in psychiatry. Serum samples were obtained without regard for timing of prior riluzole dose. Not only did this prevent us from examining peak and trough drug levels, but it may have confounded our observed serum concentrations. We did attempt to ameliorate this possibility by controlling for an approximated time between dose and venipuncture, and given the relative consistency of serum levels within subject, it is unlikely that these factors played a major role. Finally, and perhaps most importantly, peripheral concentration of drug is only a proxy for active drug in the central nervous system.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Clinical Significance

Riluzole was well tolerated by our pediatric participants, at doses of approximately 100 mg per day. This dose, and the resulting serum drug levels, are comparable to those reported for adults using riluzole for treatment of ALS. Although serum riluzole concentration varied widely across participants, it was not associated with OCD symptomatic benefit or the occurrence of adverse effects. Although our study design limited use of riluzole to treatment-refractory patients, the results of this study suggest that drug might be appropriately tested in larger doses or as a single agent in a larger cohort of youth with OCD.

Figure 1. Serum concentration of riluzole in 37 participants (89 samples)

Median dose at all visits was 100 mg/day; mean doses were 99 ± 28 , 108 ± 28 , and 120 ± 34 mg/day at weeks 24, 36, and 52, respectively. Y-axis is on the natural logarithmic scale for ease of viewing.

Figure 2. Symptom severity (CY-BOCS) versus risperidone concentration

Eighty-nine samples from $n=37$ participants. X-axis is on the natural logarithmic scale for ease of viewing. Controlling for risperidone dose [$F(1,47)=0.07$, $p=.80$], time-of-draw [$F(1,47)=0.85$, $p=.36$] and fluvoxamine [$F(1,47)=0.39$, $p=.54$], natural log-transformed serum risperidone concentration was not associated with CY-BOCS score [$F(1,47)=1.36$, $p=.25$].