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Original Article

Efficacy of Glutamate Modulators in Tic Suppression: A Double-Blind, Randomized Control Trial of D-serine and Riluzole in Tourette Syndrome

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ABSTRACT

BACKGROUND: It has been hypothesized that glutamatergic transmission may be altered in Tourette syndrome. In this study, we explored the efficacy of a glutamate agonist (D-serine) and antagonist (riluzole) as tic-suppressing agents in children with Tourette syndrome. **METHODS:** We performed a parallel three-arm, 8-week, double-blind, randomized placebo-controlled treatment study in children with Tourette syndrome. Each child received 6 weeks of treatment with D-serine (maximum dose 30 mg/kg/day), riluzole (maximum dose 200 mg/day), or placebo, followed by a 2-week taper. The primary outcome measure was effective tic suppression as determined by the differences in the Yale Global Tic Severity Scale score; specifically, the total tic score and the combined score (total tic score + global impairment) between treatment arms after 6 weeks of treatment. Mann-Whitney *U* tests were performed to analyze differences between each group and the placebo group. **RESULTS:** Twenty-four patients (males = 21, ages 9-18) enrolled in the study; one patient dropped out before completion. Combined Yale Global Tic Severity Scale score and total tic scores improved in all groups. The 6-week mean percent improvement of the riluzole (n = 10), D-serine (n = 9), and placebo (n = 5) groups in the combined Yale Global Tic Severity Scale score were 43.7, 39.5, and 30.2 and for total tic scores were 38.0, 25.0, and 34.0, respectively. There were no significant differences in Yale Global Tic Severity Scale score or total tic score, respectively, between the riluzole and placebo (P = 0.35, 0.85) or D-serine and placebo (P = 0.50, 0.69) groups. **CONCLUSION:** Tics diminished by comparable percentages in the riluzole, D-serine, and placebo groups. These preliminary data suggest that D-serine and riluzole are not effective in tic suppression.

Keywords: Tourette syndrome, tics, d-serine, riluzole, glutamate

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Introduction

Tourette syndrome is a chronic neuropsychiatric condition characterized by the presence of fluctuating motor and vocal tics. Tics vary widely in severity, and many patients require treatment to improve associated psychosocial, physical, and functional difficulties. Although current treatment strategies offer benefit to many patients, newer medicinal approaches for tic suppression are needed, given the inadequate control and adverse side effects with current therapies.[1,2]

The primary site of the brain abnormality in Tourette syndrome is unknown. Based on both direct and indirect evidence, the cortico-striatal-thalamo-cortical circuits that run from the frontal cortex to the putamen and then back to the cortex via the thalamus are likely involved. The presence of a variety of different neurotransmitters within this cortico-striatal-thalamo-cortical circuitry suggests the

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possibility that multiple neurotransmitters may be involved in the pathophysiology of Tourette syndrome. Although dopamine dysfunction has long been considered the primary abnormality, other neurotransmitters could also be implicated.[3] One potential candidate is the excitatory neurotransmitter glutamate.

Modulators of glutamatergic neurotransmission have been considered as potential therapeutic agents in Tourette syndrome based on several lines of evidence, including glutamate's essential role in cortico-striatal-thalamo-cortical circuits and proposed interactions between the glutamatergic and dopaminergic neurotransmitter systems in the prefrontal cortex, midbrain, and striatum.[4-7] Additional support for a possible role of the glutamatergic system in Tourette syndrome includes familial genetic studies and reduced postmortem levels of glutamate in the globus pallidus and substantial nigra pars reticulata.[8-11]

It remains unclear, however, if neurochemical data support a hyper- or hypoglutamatergic condition in Tourette syndrome. Mechanistically, one could hypothesize a rationale to support the benefit of either a hyper- or hypoglutamatergic state. For example, increased afferent excitation of the striatum could result from increased stimulation of glutamatergic pyramidal neurons in the prefrontal cortex, resulting in a hyperkinetic disorder such as tics. In this scenario, a glutamate antagonist may offer benefit. Alternatively, given postmortem evidence of reduced glutamate levels in the globus pallidus and substantia nigra, a glutamate agonist may be beneficial.[11,12] Given this mechanistic uncertainty, this study sought to investigate two glutamate modulators, the glutamate agonist D-serine and the glutamate antagonist riluzole.

Serine is an endogenous ligand at the glycine site of the N-methyl-D-aspartate receptor complex, an ionotropic glutamate receptor.[13,14] It has been suggested that D-serine may also act as a gliotransmitter that mediates interactions between glia and neurons.[15,16] In addition, recent studies have shown that neurons synthesize and secrete D-serine.[17] D-cycloserine, a related compound with an additional nitrogen, is thought be to a partial agonist at the N-methyl-D-aspartate receptor. Attempts to treat patients with schizophrenia and obsessive-compulsive disorder using d-cycloserine have produced variable results.[18-24]

Riluzole's mechanism is complex and not fully understood. It is thought to inhibit the presynaptic release of glutamate by blocking voltage-gated sodium channels.[25] Riluzole is US Food and Drug Administration–approved for use in amyotrophic lateral sclerosis and is being studied in a number of neuropsychiatric disorders, including childhood obsessive-compulsive disorder.[26]

In this study, we aimed to explore the efficacy of D-serine and riluzole, each compared with placebo, in children with Tourette syndrome.

Methods

Participants

All patients seen in clinic with a tic disorder were assessed for eligibility. Patients were included as follows: (1) If they met criteria for Tourette syndrome as defined by the Tourette Syndrome Classification Study Group, which includes onset before 18 years, multiple involuntary motor tics, one or more vocal tics, a waxing and waning course, the gradual replacement of old symptoms with new ones, the presence of tics for more than 1 year, the absence of other medical explanations for tics, and the observation of tics by a reliable examiner; (2) Age 8-17 years, either sex; (3) Observable tics, achieving a minimum score $\geq$22 on the Total Tic score of the Yale Global Tic Severity Scale (YGTSS); (4) Tic symptoms severe enough to warrant therapy; (5) The concurrent use of other tic-suppressing medications was permitted if the patient had been on a stable dose for more than 3 weeks and agreed to maintain a constant dosage throughout the study; and (6) Tics were not controlled with current medication or individuals were tic-suppressing drug naive.[27]

Exclusion criteria included: (1) secondary tics; (2) significant medical illness; (3) current major depression, generalized anxiety disorder, separation anxiety disorder, psychotic symptoms (based on clinical evaluation), pervasive developmental disorder, autism, intellectual disability (intelligence quotient below 70), anorexia/bulimia, or substance abuse; (4) pregnancy; (5) hypersensitivity to D-serine or riluzole; (6) baseline weight of less than 33 kg; or (7) abnormal laboratory values on baseline laboratory testing.

Study design and procedures

This was a parallel three-arm, 8-week double-blind randomized placebo-controlled treatment study in 24 children with Tourette syndrome. Each child received 6 weeks of treatment with a glutamate antagonist (riluzole), glutamate agonist (D-serine), or placebo, followed by a 2-week taper. A postintervention assessment was also performed at the end of week 8. Approval was obtained through the Johns Hopkins Institutional Review Board. Patients were randomized by the study pharmacist using a computer-generated 2:1 (glutamate modulating drug:placebo) scheme to assign patients to a study medication: riluzole, D-serine, or placebo. Medications, packaged in look-alike capsules, were distributed by the study pharmacist. The research pharmacist retained the medication codes until the completion of the study. The investigators, study coordinator, and patient/parent were not aware of the treatment assignment. A drug safety monitoring board monitored side effects and assisted in any decisions to withdraw a participant.

Medication administration

Dosage increases occurred during treatment weeks 1, 2, 3, and 4, as determined by the treating physician (HS). The starting dose of riluzole was 50 mg for 1 week; administered as one capsule every morning. If needed, as determined by the treating physician, the dose was increased weekly by 50 mg and given as a twice-daily dosage. The maximum dose used was 200 mg/day (administered as two capsules twice daily).

The starting dose of D-serine was approximately 7 mg/kg/day, given in 250- or 500-mg capsules. This was titrated weekly to a dose of approximately 30 mg/kg/day, which was also used as the maximum dose. Immediately following the treatment phase (week 6), medication was tapered over a 2-week period, with a reduction of one capsule every other day.

Evaluations

All patients underwent a screening visit that included determination of eligibility criteria and rating scales for tics: YGTSS, Clinical Global Impression-TS, and Patient Global Impression of Improvement; obsessive-compulsive problems: (Child) Yale-Brown Obsessive Compulsive Scale; attention deficit hyperactivity disorder (ADHD): DuPaul ADHD Rating Scale; depression: Depression Inventory-Short Version; and anxiety, the Multidimensional Anxiety Scale.[28-34]

Screening laboratory values included urinalysis, comprehensive metabolic panel, complete blood count, serine level, and urine b-human chorionic gonadotropin in female patients. Alternating telephone (HS) and clinic (MG) evaluations were performed weekly by blinded study physicians. Telephone evaluations occurred at the end of weeks 1, 3, and 5 ($\pm$2 days) and included discussions of clinical response, side effects, drug compliance, and medication adjustment. Patients were evaluated in the clinic at baseline at the end of weeks 2, 4, and 6. Direct clinical