Background: Severe spinal muscular atrophy (SMA) (Werdnig-Hoffmann disease, acute SMA, and SMA I) is a disease of the motor neuron characterized by onset before 6 months of age, failure ever to achieve sitting without support, and a life expectancy of 2 years or less. There is no known treatment for SMA, and, until recently, no therapeutic trials have been attempted. It is reason to believe that glutamate, an excitatory neurotransmitter, enhances programmed cell death of anterior horn cells. Riluzole, a glutamate inhibitor, has been shown to slow the rate of decline in patients with amyotrophic lateral sclerosis, another form of motor neuron disease.

Objectives: To determine whether a glutamate inhibitor might be tolerated by infants with SMA and, furthermore, whether this medication could have a positive effect on life expectancy.

Design: Subjects with homozygous deletions of the survival motor neuron gene were recruited from pediatric neuromuscular clinics and randomized in a 2:1 ratio, 2 riluzole to 1 placebo. Neurologic examination was performed at the first visit by one of the investigators. Complete blood count, hepatic and renal screens, and urinalysis were performed at baseline, 2 weeks, 1 month, 2 months, 3 months, 6 months, and 9 months after drug or placebo was started. An electrocardiogram was done at baseline, 3 months, 6 months, and 12 months. Treatment was stopped after 9 months, and blood work was repeated at 12 months. Treatment was reinstituted at 1 year if requested by the parents. The enrollment goal was 30 patients; however, support from the pharmaceutical company was withdrawn when Rhone-Poulenc Rorer was taken over by Aventis. The investigational review boards of the participating centers approved the protocol and consent forms.

Results: Seven patients received riluzole and 3 received placebo medication. All 3 patients in the placebo group died (mean age, 9 months). Three of 7 who received active drug are still living at ages 5 1/3 years, 4 years, and 30 months. None of the 10 subjects experienced adverse effects or changes in laboratory test results. None showed any change in motor abilities.

Conclusions: Riluzole appears to be safe in young children. This was a limited study with insufficient power to show a difference between the 2 groups. Because there is a suggestion of possible benefit in treated subjects, we recommend further study of riluzole in pediatric patients with SMA.

Arch Neurol. 2003;60:1601-1603
Inclusion criteria were met by patients who had SMA type I, with symptoms onset before 6 months of age and maximum motor ability no better than sitting with support. The patients had to have a homozygous deletion of the SMN gene.

The secondary outcome was mortality. We assumed that the life expectancy of all patients with SMA type I, 2 and 6 months die by age 20 months. There is no known treatment for SMA. Until recently, no therapeutic trials have been attempted.

Hypotheses regarding the pathogenesis of SMA include defective inhibition of apoptosis, glutamate cytotoxicity, and lack of neurotrophic factors in nerve or muscle. Cell bodies from bulbar and spinal motor neurons receive afferents from glutamate neurons. These neurons are, therefore, particularly exposed to glutamate, an excitatory amino acid neurotransmitter of high neurotoxic potential. The glutamate inhibitor riluzole is currently recommended for treatment of amyotrophic lateral sclerosis to slow progression of that disease.

Riluzole (Rifutek) was developed by Rhone-Poulenc Rorer, Philadelphia, Pa. Its half-life in humans is approximately 12 hours after oral administration. The compound can easily cross the blood-brain barrier.

Animal studies provided evidence that riluzole antagonizes excitatory amino acid transmitters such as glutamate. In adult rats with amyotrophic lateral sclerosis, riluzole was safe and effective in dosages of 100 and 200 mg twice daily. Minimal adverse effects in adults included asthenia, lethargy, and nausea. The present study was designed to determine whether riluzole would cause adverse effects in patients with SMA type I. The secondary outcome was mortality. We assumed that the life expectancy of all patients with SMA type I would be no more than 24 months.

### METHODS

Three clinical centers participated in this study: Cincinnati Children’s Hospital Medical Center, Shriners Hospital for Children—Portland, and Texas Scottish Rite Hospital for Children. Patients were recruited from the neuromuscular clinics at each of the institutions or referred by primary care physicians.

### RESULTS

The Table summarizes the results of the study. Ten patients were enrolled during 24 months, January 1, 1998.

### EXCLUSION CRITERIA

Exclusion criteria included weakness of the extraocular muscles, face, or diaphragm; myocardial involvement; arthrogryposis; central nervous system dysfunction; involvement of other neurologic systems or organs; hearing, vision, or sensory disturbances; or use of a mechanical ventilator (except for bilevel [biphasic] positive airway pressure [BiPAP]) at night.

### SUBJECTS

Subjects were randomized in a 2:1 ratio, 2 riluzole to 1 placebo. The dosage was calculated on the basis of body surface area, using the adult dosage of 200 mg/d, which was equivalent to 107 mg/m². For a 5-kg child whose surface area was 0.33 m², the dosage was 35 mg/d. If signs of toxic effects appeared, the dosage was decreased by 5 mg twice daily. If no signs of toxicity appeared in 3 months while taking medication, the dosage was escalated by 5-mg increments every 4 weeks. The maximum dosage was 10 mg higher than the 107 mg/m² dosage.

Riluzole was provided in 50-mg tablets by the manufacturer and sponsor of this study, Rhone-Poulenc Rorer. The pharmacist at Cincinnati Children’s Hospital Medical Center ground the tablets of riluzole into powder and placed them into capsules in 5-mg aliquots. Matching placebo capsules were prepared by the same pharmacist. Parents were instructed to open the capsules and mix the powder with soft food, such as applesauce.

Neurologic examination was done at the first visit by one of the investigators (B.S.R., S.T.I., or F.J.S.). Complete blood count, hepatic and renal screens, and urinalysis were performed at baseline, 2 weeks, 1 month, 2 months, 3 months, 6 months, and 9 months after drug or placebo was started. Treatment was stopped after 9 months, and blood work was repeated at 12 months. An electrocardiogram was done at baseline, 3 months, 6 months, and 12 months. If a child with SMA I was too ill to come to one of the participating centers to be enrolled into the study, an investigator went to see the child at the office of the referring physician. At the conclusion of the study, the parents were given the option of continuing the medication. The investigational review boards of the participating centers approved the protocol and consent forms.
to January 1, 2000; 7 patients received riluzole (group 1) and 3 received placebo (group 2). The mean age of group 1 patients at the time of diagnosis was 5.2 months; the mean age of group 2 patients was 1.2 months. The mean age at enrollment of the group 1 patients was 9.3 months, compared with 4.3 months for the group 2 patients. All group 2 patients died (mean age, 9 months; range, 6-13 months). All 3 died of respiratory complications; none were treated with BiPAP. Four of the 7 patients in group 1 died (mean age, 15.75 months; range, 5-25 months). All deaths were attributed to respiratory failure; none of these patients were treated with BiPAP. Three children taking riluzole are still living at ages 5½ years, 4 years, and 30 months. All patients are on BiPAP at night only. None of the patients showed any changes in laboratory study results, and none experienced adverse effects. None of the patients required a decrease in dosage because of weight loss, lethargy, or personality change. No evidence of cardiac, bone marrow, liver, or renal failure occurred during the study.

The surviving patients have undergone an increase of the riluzole dosage with the growth of the child; the 5½-year-old child is now receiving 75 mg/d of riluzole. None of the surviving patients have achieved the ability to sit independently when placed.

This is the first phase 1 trial of riluzole in children and the first study of use of riluzole in patients with SMA. Our conclusions must be limited as the number of subjects was small and the duration of the trial was short. Enrollment was slowed because many patients were too weak to travel to participating centers. Several parents stated that they were not interested in participating because they did not want their child to receive placebo or because they did not want to take a chance on a potentially harmful drug. Ten subjects (of an anticipated 30 subjects) were enrolled in the project before funding was withdrawn when Aventis (Bridgewater, NJ) bought Rhone-Poulenc Rorer.

All enrolled patients in the present study fit the international criteria for SMA 1, namely, onset before age 6 months and never achieving the ability to sit independently when placed. The natural course of patients with SMA 1 is such that more than 95% will die before age 2 years. The onset of symptoms was before age 6 months in all our patients. Seven of our 10 patients died before 25 months of age. The 3 patients receiving placebo died between 6 and 13 months of age. These patients had onset at or before age 2 months and followed a course similar to that of patients with severe SMA. The mean age of diagnosis of the 4 patients receiving the active medication who died was 5 months. The 3 patients taking riluzole who are still alive at the time of this report also were diagnosed at a mean age of 5 months. That these patients are alive and without mechanical ventilation except for the use of BiPAP at night only is intriguing. Certainly, these 3 patients could be following an unusual course. Despite this possibility, we believe that our unexpected results warrant a controlled trial of riluzole in patients with SMA.

The present study suggests that riluzole is safe in infants and toddlers with SMA and may have a mitigating effect on the natural course of the disease. Because the severity of SMA correlates well with the number of SMN2 copies, it would be important in future drug trials to include the copy number among patient characteristics at enrollment.

Accepted for publication May 28, 2003.

**Author contributions:** Study concept and design (Drs Iannaccone and Samaha); acquisition of data (Drs Iannaccone and Samaha); analysis and interpretation of data (Drs Russman, Iannaccone, and Samaha); drafting of the manuscript (Drs Russman, Iannaccone, and Samaha); critical revision of the manuscript for important intellectual content (Dr Iannaccone); obtained funding (Dr Samaha); administrative, technical, and material support (Drs Russman, Iannaccone, and Samaha); study supervision (Dr Samaha).

This study was funded in part by Rhone-Poulenc Rorer.

Paula Morehart, RN, provided logistical help with the project. Robert Miller, MD, referred 4 of the patients who participated in the project.

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**REFERENCES**


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