Increase of flexor reflex latency in patients with amyotrophic lateral sclerosis treated with riluzole

Recently, riluzole has been reported to increase life expectancy in patients with amyotrophic lateral sclerosis. Pharmacologically, riluzole is an inhibitor of glutamate release and a non-competitive antagonist at N-methyl-D-aspartate receptors. Glutamate antagonists are also undergoing clinical trials for several other diseases. It is known that the H reflex and flexor reflexes in experimental animals are mediated by different subtypes of ionotropic glutamate receptors; the flexor reflex by NMDA receptors and the H reflex by non-NMDA receptors. Therefore, spinal reflexes may provide an opportunity to investigate glutamatergic neurotransmission in humans in vivo. We investigated whether riluzole differentially alters the H reflex and flexor reflexes in patients with amyotrophic lateral sclerosis treated with the drug. From the natural course of the disease it is known that the density of the non-NMDA binding sites increases in the spinal cords of patients with amyotrophic lateral sclerosis. We therefore expected that treatment with riluzole would maintain the latency of the H reflex and increase the latency of the flexor reflexes.

The study was approved by the Ethikkommission of the Humboldt-University.

The H reflex (recorded from M soleus) and the flexor reflexes from M tibialis anterior were investigated in 15 controls (nine men, six women, mean age 25 years) and 10 patients with amyotrophic lateral sclerosis, at onset and after three months of treatment with 50 mg riluzole twice a day (four men, six women, age range 35–75 years; less than 30 months since the onset of clinical symptoms). The H reflex was investigated in a sitting position with stimulation of the nerve in the popliteal fossa. The flexor reflex was elicited in a sitting position with the foot mildly dorsally flexed. Stimulation was performed at the plantar aspect of the foot (20 ms duration, 50 Hz, 50 mA). The stimulus was recognized as a sharp burning pain but was tolerated by all patients and controls. The differential electrode was placed 10 cm below the patella ligament, the indistinct 3 cm distal over the tibial bone. In controls, the mean latency of the H reflex was 29.2 (SD 2.0) ms and of the flexor reflex 80.1 (SD 7.1) ms. At the onset of treatment with riluzole, the mean latency for the H reflex in patients with amyotrophic lateral sclerosis was 31.0 (SD 3.3) ms. After three months of treatment with riluzole, the latency was unchanged at 30.4 (SD 3.0) ms. The respective values for the flexor reflexes were 72.5 (SD 6.6) ms at onset and 121.1 (SD 17.6) ms (P < 0.05; fig 1) after three months of treatment with riluzole.

The latencies of the H reflex in controls and untreated patients with amyotrophic lateral sclerosis are consistent with the medical literature. The latency and pattern of the flexor reflex is similar to the report from which the method was adapted. Our results show that the H reflex and the flexor reflex are differentially affected in patients with amyotrophic lateral sclerosis treated with riluzole. The latency of the H reflex did not change in patients treated with riluzole, whereas the latency of the flexor reflex increased. This is consistent with the known pharmacological properties of riluzole as a non-competitive antagonist at NMDA receptors.

We conclude that spinal reflexes can be used to investigate the differential modulation of glutamatergic neurotransmission in situ in humans. Possibly, these diagnostic tests can be used to evaluate pharmacological therapies with glutamate antagonists.

Progressive multifocal leukoencephalopathy treated with cytosine arabinoside: 12 year follow up and postmortem findings

This patient was the subject of a previous report in 1975. We now report follow up until her death in 1985 and the postmortem examination.

Sarcoidosis was first diagnosed in 1959, at the age of 38 years, after upper gastrointestinal and a left facial palsy. She had iritis in 1965 and evidence of pulmonary sarcoidosis in 1966. Treatment was then started with prednisolone (7.5 mg daily). In 1972 she had pneumopathy and in October difficulty with the use of her right hand which slowly progressed to a right hemihyperspastic disorder, associated with facial weakness and dysphasia. A diagnosis of progressive multifocal leukoencephalopathy was confirmed by cerebro biopsy and viral culture. Within a few weeks of starting treatment with cytosine arabinoside (2 mg/kg) in September 1973 definite improvement was seen. She returned to work as a nursing tutor in November 1973. By February 1975, at the time of the first report, she was continuing with five day courses of cytosine arabinoside separated by intervals of three weeks, without complications. She continued to improve and there was at that time no evidence of speech disturbance. She had minimal right sided facial weakness, moderate spastic weakness of the right arm and hand, quite dense cortical motor deficit in the hand, and obvious cerebellar ataxia involving the right arm and hand.

In May 1975 she developed intermittent lower abdominal colic with abdominal distension and tenderness associated with nausea, flatulence, and borborygmi. A barium meal and follow through showed uniformly dilated loops of bowel and coarse oedematous mucosal folds with an abnormal mucosal pattern. Further investigations showed malabsorption of B12, iron, and folate. Biopsy showed subtotal villus atrophy. In October 1975 further gastroenterological investigations gave similar results. These gastrointestinal abnormalities have not been described with cytosine arabinoside. Glutensensitive enteropathy was confirmed by a response to a gluten free diet with considerable sustained improvement, apart from very occasional inadvertent gluten exposure, usually from gluten filler in tablets.

She had visual migrainous equivalents for many years, which only rarely proceeded to headache. Some of these attacks were associated with numbness of one or other hand, usually the right hand. In April 1976 she was having increasing attacks of migraine and found that if the right hand was affected, she became quite obviously dysphasic for an hour or more. If the numbness

Flexor reflexes in one patient at onset of treatment and after three months of treatment with riluzole (two recordings superimposed).
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