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 is mediated by NMDA receptors and the H reflex is mediated 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 flexor reflexes (from M. plantaris) were recorded 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 indifferent 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.1 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.2

We conclude that spinal reflexes can be used to investigate the differential modulation of glutamatergic neurotransmission in humans. Possibly, these diagnostic tests can be used to evaluate pharmacological therapies with glutamate antagonists.
affected the left hand, then she had some dysarthria. The association of the lateralisation of a migrainous aura with aphasia if her right hand was affected and with dysarthria if her left hand was affected is predictable, if extremely unusual, and has not been previously described.

In December 1977 she developed herpes zoster affecting the right sacral 3-5 segments. She continued to produce crops of cutaneous sarcoïd. In July 1982 there was deterioration in her mental state due to inappropriate ADH secretion requiring fluid restriction. In March 1984 she developed avascular necrosis of the left shoulder due to steroids and in January 1985 she had a left shoulder prosthesis. In September 1985 she developed a febrile illness with rapid deterioration, she lapsed into coma and died.

A necropsy carried out by Dr WL Brander showed that the cause of death was acute pyelonephritis with septicaemia. No evidence of pulmonary sarcoïdosis was found. The brain weighed 1272 g. The leptomeninges over the frontal convexity were mildly opaque and thickened. There was a small old contusion in the orbital surface of the right frontal lobe. The old biopsy site in the left hemisphere was marked by a 1.5 cm diameter defect with underlying scarring (fig 1A). The lateral ventricles, including the temporal horns, were enlarged, as was the third ventricle. In the white matter, there were numerous irregular grey, slightly depressed lesions in both hemispheres (fig 1B), the largest measuring 1.8 x 1 cm. In the left frontal lobe the lesions were shrunken and cavitated.

The corpus callosum and periventricular regions were well preserved. Similar lesions were also seen in the right putamen and left thalamus. The cortex was relatively well preserved. The cerebellum, brainstem, and spinal cord appeared normal. Histological examination showed that there were large and small poorly demarcated pale lesions in the white matter of burst out progressive multifocal leuкоencephalopathy. They were sparsely cellular, containing astrocytes, some with large bizarre nuclei containing PAS positive inclussions (fig 2A). However, immunocytochemistry for JC virus failed to reveal the Papova virus antigen. Sections from the patient's earlier biopsy demonstrated the presence of the viral antigen when stained with the same antibody. No viral particles were seen in postmortem tissue taken for electron microscopy as had been found in the biopsy.1 The lesions involving the deep grey matter looked similar.

In addition there was widespread meningoecascular sarcoïdosis (fig 2B). Loose granulomata composed of epitheloid cells, lymphocytes, plasma cells, and multinucleated giant cells were present in the leptomeninges and in the walls of meningeal veins and arteries. The inflammation was more severe in the region of the biopsy site and extended into the underlying scarred brain. In the cerebellum, there was patchy cortical scarring related to the meningeal sarcoïd. There was no degeneration of the long tracts of the brainstem and spinal cord. Re-examination of the earlier biopsy showed mildly thickened leptomeninges but no evidence of sarcoïdosis.

Progressive multifocal leuкоencephalopa-thy typically has a fatal outcome, usually within six months. Rare exceptions include a patient also with coeliac disease, who died 10 years after the onset of the illness, and another with lymphosarcoma and progressive multifocal leuкоencephalopa-thy for five years who seemed to have periods of clinical remission.3

There has been considerable increase in interest in the management of patients with this condition in recent years because of the AIDS epidemic. The response to cytarabine or carbovir is usually disappointing. Most reported patients have only received one or two courses of five days. This patient was given an unusual drug regime with five day courses of intravenous cytosine arabinoside at three weekly intervals for a year and the intervals were slowly extended to two months over a second year and to three months for the third year. She had her last course of treatment in May 1978, just over three years from the first treatment. This programme was devised because it did not seem likely that cytarabine would eliminate the virus completely from the nervous system and her immunosuppressed state persisted throughout this time.

The pathological evidence indicates cure from progressive multifocal leucoencephalopathy, which has not been claimed before. Cytosine arabinoside seems to have affected this cure, as her condition deteriorated progressively until treatment was started and improvement occurred soon afterwards.

We are grateful to Dr WL Brander, who kindly sent the brain to us for examination and to Dr Herbert Budka who performed the immunocytopathology.

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Brain and spinal cord MRI in motor neuron disease

In your September issue, Thorpe et al. describe their MRI findings in 11 patients with motor neuron disease. They found symmetric areas of high signal intensity on T2 weighted images within the corticospinal tracts, as previously reported by other investigators. We reported a case of amyotrophic lateral sclerosis with further high signal intensity in fibres of the corpus callosum on proton density and T2 weighted images, closely matching findings of earlier pathological reports. We would be interested to know if Thorpe et al found similar callosal signal abnormalities in some of their patients. These findings would enhance the diagnostic role of MRI in patients with suspected motor neuron disease, as suggested by the authors.

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Thorpe et al reply
We thank Van Zandijcke and Casselman for bringing their case to our attention and confirm their findings. We noted the severe loss of cerebellar white matter and found high signal in the corpus callosum in
Progressive multifocal leucoencephalopathy treated with cytosine arabinoside: 12 year follow up and postmortem findings.

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