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Spinal cord protection using riluzole

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Adrian Mellor

Keywords

Aortic surgery, NMDA receptor antagonists, reperfusion injury, riluzole, spinal cord injury

Comments

This study provides both clinical and histological evidence of marked improvement in outcome after spinal cord ischemia. The safety of high doses of riluzole are not discussed in the paper and may be of significance. The results of the use of this drug to prevent paralysis after thoracoabdominal aortic surgery should be keenly awaited.

Introduction

Spinal cord ischemia leading to paraplegia remains a common and devastating complication of thoracoabdominal aortic aneurism repair. Recent evidence suggests that release of excitatory amino acids are involved in the development of ischaemic injury. Glutamate is thought to play an important role in the development of ischaemic injury through its action on N methyl D aspartate (NMDA) receptors and non-NMDA receptors by inducing sodium and calcium fluxes into the cell and cell death. Currently available NMDA receptor antagonists are toxic and unsuitable for clinical use. Riluzole is a neuroprotective drug that inhibits sodium and calcium channels and activates a new class of potassium channels. It is also a non competitive NMDA receptor blocker. The drug has been shown to have anti-ischaemic properties in several models and is in clinical use in patients with amyotrophic lateral sclerosis.

Aims

The aim of the study was to determine whether administration of riluzole before or after aortic cross clamping is capable of preserving the structural integrity of the spinal cord after severe ischemia.

Methods

Female New Zealand white rabbits were used as the model in this study. The animals were monitored to ensure hemodynamic stability throughout the study period. After the clamps had been on for 40 min the animal's abdomen was closed and randomly assigned to one of four groups. One group had a sham procedure (ie opened and closed without clamping the aorta). These animals were killed after 3 h. The three other operative groups were randomly assigned to be killed at 24, 48 and 120 h. Spinal cord sections were removed and prepared as histological sections. The rabbits were allocated to five treatment groups: sham operation receiving 8 mg/kg riluzole (n = 3); group A 8 mg/kg riluzole 30 min before aortic occlusion; group B 4 mg/kg riluzole 30 min before aortic occlusion and at onset reperfusion; group C 8 mg/kg riluzole at onset of reperfusion. Group D received saline 30 min before occlusion. Neurological outcome was graded according to a standard scale 0 (no movement) to 5 (normal movement). The histological sections were either prepared as cryostsat specimens (L6-7 sections) or paraffin specimens (L4-5). The neuropathologist examining the sections was blinded as to the timing and dose of drug used. Tissues were further prepared for histopathological sections and immunohistochemical stains for microtubular-associated protein-2.

Results

At 24 h after ischaemia all rabbits in the control group showed paralysis. Those treated with riluzole were markedly better. The results were best in the rabbits which received riluzole 4 mg/kg 30 min before cross clamping and on reperfusion. Of this group, 80% had normal neurological scores. There were no significant differences in hemodynamic variables across the groups. Histopathological examination was used to detect necrosis of the spinal cord. All the rabbits in the control group showed evidence of necrosis but those in group B had spinal cords that appeared comparable to those in the sham operation group. Terminal deoxynucleotidyltransferase-mediated deoxyuridine triphosphate-biotin nick end label staining was used to characterise apoptosis. Animals treated with riluzole showed no evidence of necrotic motor neurons with this technique whereas the control animals had >50% cell death. Immunohistochemical techniques were used to stain the cytoskeletal elements of the spinal cord. Rabbits in the control group showed marked proteolysis after 24 h and riluzole attenuated this response.

Discussion

It seems likely that excitatory amino acids and specifically glutamate act as potent neurotoxic agents during periods of ischemia. Excitation of NMDA and non-NMDA receptors leads to a rise in intracellular calcium that triggers proteases, lipases, protein kinase C, nitric oxide synthetase, endonucleases, altered gene transcription and release of free radials leading to neuronal injury and death. Riluzole is known to be neuroprotective but the receptor basis for this is unknown. It may well be that the drug inhibits presynaptic glutamine release which is probably linked to riluzole's capacity to inhibit sodium and calcium ion voltage sensitive channels and to activate a new class of background potassium channels that are highly expressed in the spinal cord. This study shows that riluzole prevents cell death, apoptosis and improves clinical outcome in severe spinal cord ischemia. A potential source of error is that riluzole causes a decrease in body temperature which may, in itself, account for improved

neurological outcome. However, in this study temperature was measured and found not to vary between the groups. The drug has been used since 1995 with an acceptable side effect profile although at a much lower dose (100-200 mg/day). The place for this drug may be preventative in elective aortic surgery or to stabilise the neuronal loss in the case of emergency procedures.

References

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