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Edaravone Administration and its Potential Association with a New Clinical Syndrome in Cerebral Infarction Patients: A Case Report

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Abstract

BACKGROUND

Edaravone is a widely used treatment for patients with cerebral infarction and, in most cases, edaravone-induced side effects are mild. However, edaravone-related adverse reactions have been receiving increasing attention.

CASE SUMMARY

Edaravone is a widely used treatment for patients with cerebral infarction and, in most cases, edaravone-induced side effects are mild. However, edaravone-related adverse reactions have been receiving increasing attention.

CONCLUSION

Our cases highlight the importance of educating clinicians regarding the new edaravone-induced clinical syndromes of cerebral infarction as potentially fatal adverse drug reactions. Considering that no laboratory or confirmatory test exists to diagnose edaravone-induced death from cerebral infarction, clinicians' knowledge is the key element in recognizing this phenomenon.

INTRODUCTION

Edaravone is a clinically effective neuroprotective agent and a free radical scavenger that can capture hydroxyl radicals. It was approved for marketing in Japan and China in 2001 and 2005, respectively. Initially indicated for protection against ischemic brain damage, edaravone's indications have gradually expanded to the treatment of amyotrophic lateral sclerosis [2-5]. However, owing to its widespread clinical application, adverse reactions to edaravone have also received increasing attention [6-8]. In the earliest randomized controlled trial of edaravone for ischemic stroke treatment, 4 patients in the edaravone and 5 patients in the blank control groups died out of the 125 cases in each group. In the edaravone group, all deaths were caused by cerebral infarction; while in the control group, three patients died of cardiac arrest, pneumonia, and depression suicide, and two patients died of cerebral hernia caused by edema, worsened cerebral infarction, pneumonia, and disseminated intravascular coagulation (DIC) caused by cirrhosis [6]. In 2007, Japanese scholars reported that one patient with cerebral infarction treated with edaravone experienced severe adverse reactions. The patient presented with a sudden disturbance of consciousness and shock 12 days after hospitalization [6]. In 2018, we observed three patients who died of sudden worsening of acute cerebral infarction during treatment with edaravone, which was the suspected cause.

CASE PRESENTATION

Chief complaints

Case 1 A 63-year-old woman with slurred speech and mental and behavioral abnormalities for ten days was admitted to our hospital.

Case 2 A 65-year-old man was admitted to our hospital due to being unconscious for 11 hours.

Case 3 A 71-year-old man was admitted to our hospital due to sudden twisting of the left side corners of his mouth for more than five days and difficulty swallowing for two days.

History of present illness

Case 1 A 63-year-old woman with slurred speech and mental and behavioral abnormalities for ten days was admitted to our hospital.

Case 2 A 65-year-old man was admitted to our hospital due to being unconscious for 11 h.

Case 3 A 71-year-old man was admitted to our hospital due to sudden twisting of the left side corners of his mouth for more than five days and difficulty swallowing for two days.

History of past illness

Case 1 No significant history of past illness was noted in the patient.

Case 2 The patient had a history of hypertension, diabetes mellitus, and cerebral infarction

Case 3 The patient had a history of hypertension.

Personal and family history

Personal history and family history are not special

Physical examination

Case 1 On admission, the patient's vital signs were stable. The patient showed dysarthria, lack of cooperation, level V muscular strength in both limbs, and negative Babinski signs in both limbs.

Case 2 temperature, 36.6 °C; blood pressure, 175/91 mmHg; heart rate, 80 beats/min; and respiratory rate, 16 breaths/min. The patient was in a superficial coma state. The left nasolabial fold was slightly shallower than the contralateral side. Upon pain stimulation, the patient responded with an expression of pain and lifted his left limbs from the bed surface, but not the right limbs. Muscle tone of the right limb was lower than that of the left limb. Tendon reflexes on the right side were weaker than those on the left side.

Case 3 On admission, the patient's vital signs were stable. The patient was alert and had symmetrical forehead lines and dysarthria. The right nasolabial fold was slightly shallower than its contralateral part, and the patient's tongue deviated to the right when it was protruded. The patient had normal muscular strength and tone in all four limbs and symmetrical sensation and tendon reflexes. Bilateral Babinski signs were negative.

Laboratory examinations

Case 1 Laboratory examinations, including routine blood tests, liver and kidney function tests, and electrolyte and blood coagulation tests were within normal parameters. Electrocardiography revealed normal sinus rhythm.

Case 2 Examination of blood coagulation status, liver and kidney function, and electrolyte levels after admission revealed no obvious abnormalities. Electrocardiography revealed normal sinus rhythm.

Case 3 Laboratory examinations were within normal parameters. Electrocardiography revealed normal sinus rhythm.

Imaging examinations

Case 1 Head CT scan showed cerebral infarction in the bilateral parietal lobes with multiple small ischemic lesions.

Case 2 The patient's emergency head CT scan showed cerebral infarction in the left thalamus and right cerebellar hemisphere.

Case 3 Head CT scan suggested a probability of lacunar infarction in the left brainstem.

FINAL DIAGNOSIS

Case 1 Acute cerebral infarction, Respiratory failure, and Pneumonia

Case 2 Hypertension, Diabetes mellitus, and Cerebral infarction.

Case 3 Hypertension, DIC, and Cerebral infarction.

TREATMENT

Case 1 The following drugs were prescribed: aspirin (100 mg once a day) [7-8], atorvastatin (20 mg once a day) [8-9], edaravone (30 mg twice a day), and *Ginkgo biloba* extract [10-11]. On the sixth day after admission, the patient developed dyspnea and had decreased oxygen saturation. The patient was transferred to the intensive care unit (ICU) for tracheal intubation and mechanical ventilation. Multiple ecchymoses were observed on the patient's body. Disseminated intravascular coagulation (DIC) was diagnosed based on blood coagulation results, and low-molecular weight heparin (0.2 ml twice a day), tranexamic acid (500 mg once a day), fresh frozen plasma (400 mL), and cryoprecipitate (6 U) were administered to the patient. Blood coagulation status improved gradually after the treatment. The patient's respiratory condition improved after receiving ceftizoxime, and she was released from the ventilator.

Case 2 aspirin (100 mg once a day) [7-8], atorvastatin (20 mg once a day) [8-9], edaravone (30 mg twice a day), *Ginkgo biloba* extract [10-11], and ceftizoxime (2 g three times a day) to treat the lung infection. Insulin was pumped intravenously based on increased blood glucose levels.

Case 3 clopidogrel bisulfate (75 mg once a day), atorvastatin (20 mg once a day) [8-9], edaravone (30 mg twice a day), and ozagrel extract.

OUTCOME AND FOLLOW-UP

Case 1 On the 10th day after admission, the patient experienced sudden cardiac and respiratory arrest. After external chest compressions and mechanical ventilation, her heartbeat and breathing were restored. However, two further cardiac arrests occurred, and the patient died after the last attempt at resuscitation failed.

Case 2 On the third day after admission, the patient's consciousness improved into lethargic state. However, on the fifth day after admission, the patient lapsed into a deep coma state and his heart rate decreased gradually. Resuscitation attempts were ultimately unsuccessful.

Case 3 The twisted corners of the mouth improved rapidly. However, sudden cardiac arrest occurred. The heartbeat was restored after external chest compressions, and the patient was alert again. During transfer to the ICU, his heart rate slowed down to 20 beats/min but was restored after external chest compressions. A bedside tracheotomy was performed due to difficulties with orotracheal intubation. Bleeding at the cutting site and urethral bleeding occurred. The coagulation function showed prothrombin time 15.3 s, increased prothrombin time ratio 1.30, increased international normalized ratio 1.31, decreased prothrombin activity 65.2%, activated partial thromboplastin time 32.6 s, thrombin time 18.1 s, and increased D-dimer >76 mg/L. Fresh frozen plasma (400 mL), cryoprecipitate (6 U), and red blood cell suspension (2 U) were administered to the patient. Compression and carbazochrome sodium sulfonate injection were performed to stop the bleeding, and the patient's bleeding improved. However, six days after admission, the patient experienced cardiac arrest and died.

DISCUSSION

Edaravone is a newly developed free radical scavenger, and its administration has been used as a clinical therapeutic option for the management of cerebral infarction [6]. In this case, all three patients had acute cerebral infarction. Therefore, we selected edaravone as the therapeutic option for our patients.

The instructions for edaravone clearly suggest that caution should be exercised when using the drug in cardiac patients due to the risk of death [14]. When edaravone was prescribed to elderly patients with cerebral infarction, some experienced a sudden worsening of their condition or died of cardiac arrest [15]. Therefore, we suspected that edaravone may cause serious adverse reactions, although the reason for this remains unknown. Death in patients with cerebral infarction is commonly caused by cerebral hernias in the acute phase of cerebral edema and organ dysfunction resulting from infection accompanied by the deterioration of the underlying heart disease [16-17]. This is a noteworthy aspect that should be emphasized, as the acute ischemic stroke etiology in the patients described may also be due to hematological disease [18]. However, in

three cases, the patients' condition deteriorated suddenly and they passed away soon after, which is different from the common cause of death we mentioned above. All these cases had the following characteristics: 1. elderly patients (aged > 60-year-old), 2. Patients with acute cerebral infarction but with a small infarct size, no increase in intracranial pressure, and no serious infection; 3. No history of coronary heart disease, no atrial fibrillation or heart failure, and no abnormal electrocardiography; 4. treatment with edaravone for 4-10 days; 5. rapid deterioration in the patients' condition, including coagulation dysfunction, severe hepatic and renal damage, or sudden cardiac arrest; and 6. poor response to treatment and difficulty in recovering.

Edaravone has also been reported to cause coagulation dysfunctions. In Japan, approximately 400,000 patients received edaravone within 4 years of its release in 2001. The registered adverse reactions were 477 cases, including hepatobiliary diseases (0.1%), renal urinary diseases (0.05%), and thrombocytopenia/DIC (0.02%) [5, 6]. Both cases 1 and 3 showed coagulation dysfunction, which improved with plasma and cryoprecipitate infusion, and edaravone was discontinued. This suggests that coagulation dysfunction may have occurred before and after cardiac arrest in these aggravated conditions. Therefore, early detection and reasonable treatment of coagulation dysfunction are important. Patients showed tracheal hemorrhage after tracheotomy, massive urethral hemorrhage, and an abnormal coagulation index without a significant decline in platelets, which were in line with the serious adverse reactions of edaravone with a high risk of disseminated or diffuse intravascular coagulation.

Cardiac arrest occurred in all three patients during treatment with edaravone. In cases 2 and 3, cardiac arrest was the only manifestation of early exacerbation. Patients 1 and 3 were successfully resuscitated after short-term cardiac arrest, but all three patients ultimately had a worse prognosis. Because none of the three patients had prior heart disease, the cardiac arrest could not be attributed to existing heart disease. Based on our clinical observations, other possible causes of the three deaths could be excluded, including concomitant medications such as aspirin, clopidogrel, atorvastatin, Ginkgo

biloba extract, ozagrel extract, and ceftizoxime. There were no severe adverse reactions related to sudden cardiac arrest, and there were no warnings for medications for patients with heart disease according to the instructions for these drugs. Therefore, these drugs are unlikely to cause disease progression or cardiac arrest. During this exacerbation, severe hepatic and renal function impairments were observed in case 3, which have been mentioned as severe adverse reactions caused by the edaravone. Therefore, the sudden deterioration of the patients may be due to adverse drug reactions to edaravone. However, the cause-and-effect relationship between the three patients' deaths and edaravone's severe adverse reactions still requires confirmation.

In contrast, experimental animal studies have suggested that edaravone treatment improves hepatic injury following ischemia/reperfusion injury, partial hepatectomy, or endotoxin administration [19]. Other researchers have shown that edaravone has beneficial effects on kidney injury induced by ischemia/reperfusion or cisplatin[20-22]. It is possible that edaravone and edaravone-peroxy radicals, which are metabolic products of edaravone, are responsible for these adverse effects; however, the underlying mechanisms remain unclear. Further studies are required to determine the discrepancies between the protective effects observed in previous animal studies and the adverse effects observed in our patients.

CONCLUSION

In summary, these patients exhibited similar clinical characteristics. Although the characteristics of edaravone use that may lead to sudden death have not yet been identified, this series of cases represent a new clinical syndrome. Thus, further studies are needed to characterize the pathophysiology of this syndrome and determine the underlying causes.

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