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Case Report

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Can Amantadine Cause Resistant Hypernatremia in the Treatment of Hypoxic Brain Injury due to Cardiac Arrest?

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ABSTRACT

Out-of-hospital cardiac arrest complicated by neurological deterioration leads to a worse prognosis. Therapeutic hypothermia is the primary treatment to indicate utility in improving survival as well as limiting neurological damage in cardiac arrest patients. A 56-year-old male patient, not to be treated with therapeutic hypothermia, received more than 45 minutes of cardiopulmonary resuscitation but had significant damage as a result of hypoxic brain injury. We present a case of treatment-resistant hypernatremia, which was thought to be due to a neuroprotective agent used in hypoxic brain injury treatment and was not previously mentioned in the literature.

Keywords: Amantadine, cardiac arrest, hypernatremia, hypoxic brain injury

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INTRODUCTION

The pathogenesis of hypoxic-ischemic encephalopathy has been associated with a complete lack of oxygen to the brain and the death of brain cells due to hypoxia,[1] which is a leading cause of mortality and morbidity among those undergoing cardiac arrest. Apart from the standard intensive care treatment modalities, pharmacological treatments have been tried. Amantadine is an antiviral agent with anti-Parkinsonian activity and the mechanism of amantadine, one of the neuroprotective agents, is yet not exactly understood but it is thought that qua they block the receptors to limit the uptake of dopamine.[2] In clinical practice, especially in traumatic brain injuries with prolonged disorders of consciousness, amantadine has been used with reasonable success and is indicated in the treatment of drug-induced extrapyramidal reactions. Serious adverse effects contain neuroleptic malignant syndrome, psychosis, and central nervous system depression. Attention to usage is necessary for patients who developed heart disease, and hepatic and kidney impairment. Here we aim to present a 56-year-man with acute brain hypoxia secondary to cardiac arrest, in whom amantadine is thought to be reason of resistant hypernatremia.

CASE PRESENTATION

A 56-year-man with a previous history of hypertension and an active smoker of 20-25 cigarettes per day was transferred to our institution following a witnessed cardiac arrest on a street. After basic cardiopulmonary resuscitation (CPR) maneuvers were performed for 10 minutes, he underwent CPR for over 45 minutes at an emergency department. Adrenaline (1 mg) was administered 3 times every 3 minutes and a return of spontaneous circulation (ROSC) was obtained with ST elevation electrocardiogram in V1 and ST depression in V2. Heart rate was 120 beats per minute and regular and blood pressure was 90/60 mmHg. No inotropic support to maintain the circulation was administered. Percutaneous coronary intervention (PCI)

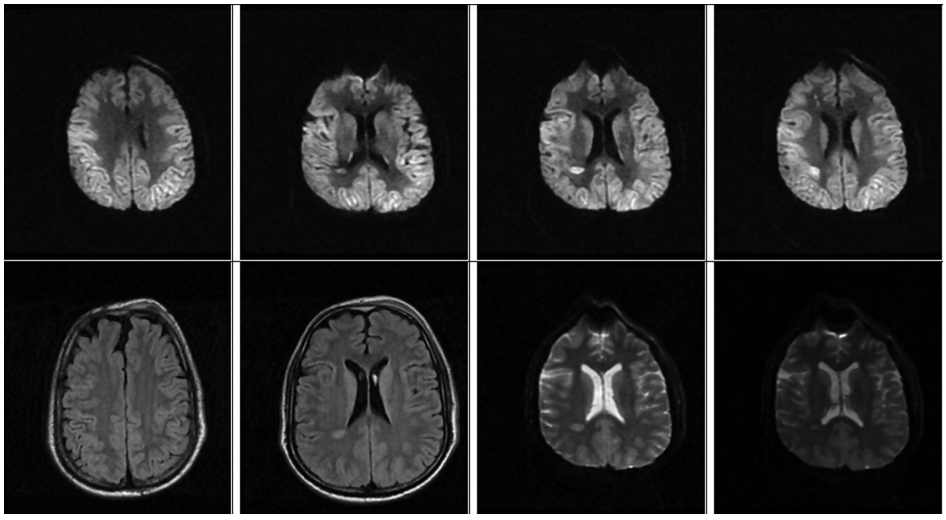

Figure 1. 13 × 19 mm hyperintense lesion on T2-weighted magnetic resonance was observed in the right posterior periventricular white matter, and diffusion restriction was observed in this localization. Diffusion restriction was observed in the bilateral hemispheric cortical parenchyma, and the findings may be significant in terms of global hypoxic ischemia.

was performed for evaluation of the cause of the cardiac arrest, which showed an occlusion of the proximal segment of the right coronary artery (RCA), and a drug-eluting stent was implanted in RCA. After PCI, the patient was taken to the intensive care unit (ICU) with mid-dilated pupils, +/+ light reflex, intubated and unconscious with a Glasgow Coma Scale (GCS) score of 3 (E1VTM1) without any sedative medication. At the ICU admission, the patient was on mechanical ventilation, FIO_2 of 40%, with vital signs of blood pressure 110/50 mmHg, temperature of 37.2°C, respiratory rate of 25 cycles/minute, and O_2 saturation of 95%. Laboratory findings at presentation revealed the following values: white blood cells 7450/µL, hemoglobin 15.2 g/dL, platelets 532,000/µl, sodium 139 mEq/L, potassium 4.6 mEq/L, chloride 101 mEq/L, blood urea 31 mg/dL, and creatinine 1.06 mg/dL. Arterial blood gas tests showed pH 7.42, pCO_2 36.4 mmHg, bicarbonate 24 mmol/L, and lactate 1,2 mmol/L. Computed tomography did not reveal intracerebral edema in the acute period. Diffusion-weighted magnetic resonance imaging performed on day 2 revealed a finding in favor of global hypoxic-ischemic encephalopathy (HIE) (Figure 1). The patient was diagnosed as having HIE and amantadine intravenous infusion therapy was initiated at 200 mg/day (PK-MERZ®, Merz Pharmaceuticals, of Frankfurt, Germany) and the dosage was adjusted according to the glomerular filtration rate. However, amantadine therapy had to be ceased on day 6 upon the observation of resistant hypernatremia. The patient's plasma sodium level raised gradually to a level of 167 mEq/L on day 6 of amantadine treatment, from a level of 138 mmol/L prior to initiating amantadine (Figure 2). The values on sixth day urine were sodium <20 mmol/L, plasma potassium 5.8 mEq/L, plasma chloride 119 mEq/L, blood urea 171 mg/dL, creatinine 3.06 mg/d L, plasma glucose level 150 mg/dL, serum osmolality 372 mOsm/kg, urine density 1020 mg/L, and the patient's urine output was below 0.5 mL/kg/h for 72 hours. By day 6, the cumulative average fluid balance was 8 L. Despite of the water through a nasogastric tube and 5% dextrose, plasma sodium levels gradually increased. Drug treatment (including anti-edema) that was proven to cause hypernatremia was not administered to the patient during the hospitalization period and on day 6 amantadine was discontinued and sodium levels returned to normal within 4 days with the same hydration therapy, while creatinine values increased. In the follow-up, he had a second cardiac arrest, and CPR was initiated; however, ROSC was not achieved and was declared dead after 14 days of his hospitalization.

MAIN POINTS

- Case reports and observational analyses showed that amantadine used as a neurostimulant in patients with prolonged disorders of consciousness is associated with improved consciousness among patients with different types of non-traumatic brain injury.
- The possible side effects of amantadine may include orthostatic hypotension, peripheral edema, hallucinations, xerostomia, drowsiness, blurred vision, psychosis, and neuroleptic malignant syndrome.
- Amantadine can cause hyponatremia as a result of the Syndrome of Inappropriate Antidiuretic Hormone; however, in the literature review, it was not shown that amantadine can cause hypernatremia.
- Since hypernatremia started with the initiation of amantadine in this case and the sodium values of the patient returned to the normal range after amantadine was discontinued, we thought that this situation might be due to amantadine.
- We would like to emphasize that if hypernatremia develops in cases where amantadine is used, it should be kept in mind that this may be drug-related.

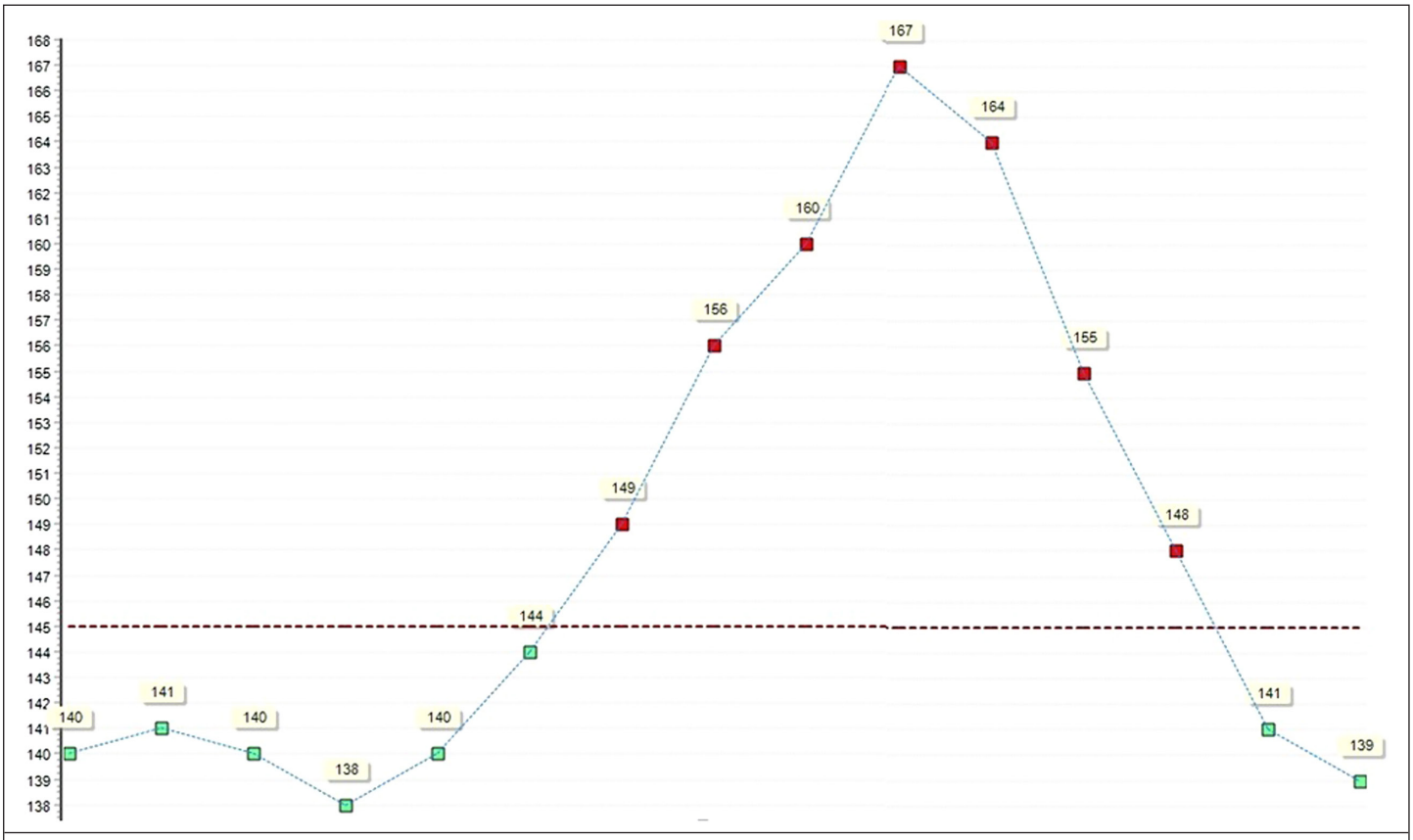

Figure 2. Line graph showing changes in the blood serum sodium levels.

DISCUSSION

The glutamatergic system, which is one of the neurotransmitter systems in the central nervous system, suppresses wakefulness. Amantadine, a glutamate antagonist, increases wakefulness by helping to decrease N-metil-D-aspartat (NMDA)-related calcium channel-dependent postsynaptic membrane excitation in the target neuron by using the glutamatergic pathway. Because of these properties, amantadine is used as an emergency and intensive care treatment in severe and life-threatening cases of Parkinson's disease and during acute exacerbation of symptoms, and to increase alertness and sensory perception (as an adjunct treatment agent in coma patients of various origins; traumatic brain injury/surgery, post-anesthetic awakening, hypoxia, infarction, bleeding, trauma, or infection).

The first clinical use of amantadine in patients with impaired consciousness was in 1988. Chandler et al[3] observed significant clinical improvement following the initiation of amantadine in 2 patients with aggression and agitation due to acute traumatic brain injury. In a prospective study conducted by the same team 1 year later, an acceptable level of positive improvement was observed in 14 of 30 patients, despite significant side effects in 5 of them.[4] A study noticed improved executive function with high-dose amantadine therapy that is not often administered in chronic traumatic brain injury patients.[5] Contrary to positive studies, a clinical trial of 40 traumatic brain injury patients taking amantadine for 6 weeks did not find any positive impact on neurological prognosis.[6] Aksu et al[7] administered 200 mg/day amantadine treatment to a patient with a prediagnosis of meningoencephalitis whose consciousness did not improve despite antibiotic treatments and on the third day, they observed that the patient's state of consciousness improved and the GCS increased from 7 to 10. Lehnerer et al[8] observed a stunning awakening of the patient with subarachnoid hemorrhage caused by a rupture of a right-sided middle cerebral artery aneurysm fully orientated after starting amantadine treatment within days.

Our patient developed hypernatremia which we could not understand, after starting the drug. We conducted research on the etiology of hypernatremia in this patient. Extensive urine and blood analysis were performed. When the content of amantadine was assessed, it was observed that it contains sodium ions. Sodium content in 500 mL of infusion solution of the drug is 1770 mg. Oral proton pump inhibitor, subcutaneous anticoagulant, enteral nutrition solutions with the lowest sodium content, sodium-free hydration fluids given orally and intravenously in the period when the sodium value is high, antibiotic therapy revised according to the culture results (colimycin, Piperacillin, tazobactam, and Linezolid) and norepinephrine infusion was ordered to the patient. Bicarbonate infusion, which may cause hypernatremia, or the

sodium-containing solution was not replaced in the patient during the period in which the sodium values of the patient exceeded the threshold value. Fluid replacement containing enough sodium to cause hypervolemic hypernatremia was not applied to the patient with a positive cumulative balance. There was no response to hypoosmolar fluid replacements given to reduce sodium values. As a result of the examinations performed on the patient for the causes of hypernatremia it was thought that the hypernatremia might be due to amantadine-containing sodium as the sodium value rapidly decreased after the drug was discontinued. Diabetes insipidus is the most common cause of hypernatremia in such a patient. Despite the hypernatremia that developed in the patient, the diagnosis of diabetes insipidus which may develop due to HIE was ruled out because polyuria was not observed and the urine density was not low.

CONCLUSIONS

The literature review was conducted on the relationship between amantadine and hypernatremia; however, there is not any data regarding this. Therefore, we cannot say that the cause of hypernatremia is definitely drug-related, and we wanted to add a question mark to the title, but it should be kept in mind that the drug may be the cause in cases of unexplained hypernatremia treated with amantadine.

Informed Consent: Informed consent from patients had been waived by the institutional review board because there was no change in patient management and patient identifiers were delinked from the analysis.

Peer-review: Externally peer-reviewed.

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