Fatal Intoxication Using Amantadine and Pramipexole in a Uremic Patient

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Abstract- We report a fatal intoxication in a 59-year-old woman who had uremia undergoing hemodialysis, and then took amantadine and pramipexole for Parkinsonian tremor. Toxic manifestation includes myoclonus, ataxia, confusion and sudden death. This report highlights the fact that using amantadine and pramipexole may be fatal in patients with uremia even undergoing hemodialysis.

Key Words: Uremia, Amantadine, Pramipexole

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INTRODUCTION

Amantadine is commonly used in treatment of Parkinson's disease. Though rare, fatal intoxication using amantadine has been reported in uremic patients[1-3]. Pramipexole is a new non-ergot dopamine agonist. Its dose should be adjusted in these patients because it is excreted mainly by kidneys[4]. Herein we report a fatal intoxication in a uremic patient after the use of amantadine and pramipexole for a period of time. In addition to describing the detailed clinical course, this report is intended to remind neurologists of the risk of sudden death in using both drugs to treat uremic patients.

CASE REPORT

The patient was a 59-year-old uremic woman being treated with regular hemodialysis for 4 years. She came to the neurology clinic because she had been troubled by hand tremor for one month. Parkinsonian tremor was considered, and therefore pramioexole 0.125 mg three times a day was prescribed for treatment for the first week. Tremor was just mildly improved. Pramipexole was then titrated to 0.25 mg in combination with propranolol 10 mg three times a day. She returned to clinic two weeks later and still complained of tremor. Amantadine 100 mg twice a day was therefore added and the dose of propranolol was doubled. One week later, at the third visit, she said her tremor was improved. However, she did not mention that she had ataxic gait after the use of amantadine. Four days later, she was brought to the emergency room because of severe general malaise. She spent a sleepless night in the emergency room waiting for admission and a bed.

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Next morning, when she arrived in ward, her consciousness was clear. She had no fever, no tachycardia, but showed a mildly high blood pressure (188/94 mmHg). Neurological examination revealed generalized areflexia and no dysfunction of the cranial nerves. In spite of full muscle power, she was experiencing difficultly in walking and standing. Intermittent spontaneous generalized myoclonus was noted. Intention tremor was shown by the finger-nose-finger test. Heel-knee-shin test also revealed ataxia and dysmetria of both legs. When she tried to get up from bed, she showed an exaggerated action tremor of her trunk and limbs. These neurological findings were interpreted as related to metabolic or toxic encephalopathy presenting with myoclonus and cerebellar ataxia. Laboratory findings were not remarkable except anemia (hemoglobin = 7.4 g/dl) and elevated creatinine (5.5 mg/dl). Serum potassium level was 4.4 mEq/L on admission. Glutamic pyruvic transaminase (GPT) was 28 U/L. Brain magnetic resonance imaging showed nonspecific white matter change. After the above examinations, medications were considered to be the culprit of the toxic encephalopathy. Therefore, pramipexole was discontinued and amantadine was reduced to 100 mg per day.

First night post-admission, she remained sleepless. Next morning, before taking 100 mg of amantadine, she became mildly confused: mistaking breakfast for lunch. Otherwise, neurological condition was similar to that of the prior day. About noon, she appeared irritable and she could not recognize her son. Half hour later, she had one episode of upward gazing and suddenly became motionless. Her son thinking that she was tired and exhausted did not inform doctors immediately. At about 2:50 pm, a nurse found the patient deceased. Emergent cardiac sonography performed immediately after resuscitation showed no impairment of cardiac contractility.

DISCUSSION

Amantadine may induce some insignificant adverse effects in patients with normal renal function, but fatal intoxication would occur in uremic patients because amantadine is minimally dialyzable. Victor et al reported the mean half-life of elimination of amantadine during chronic hemodialysis was 8.3 days (ranging from 7.0 to 10.3 days). Less than 5% of the dose was removed by 4-hour hemodialysis[5]. Ing et al reported a uremic patient undergoing hemodialysis suddenly died after taking amantadine 200 mg per day for one week[1]. Simpson and colleagues also reported a patient who died after taking amantadine 200 mg per day for ten days, but renal function was not documented in that report[2]. Even in patients with normal renal function, death may happen due to acute overdose[3]. Cardiac arrhythmia was considered as the most possible cause of sudden death[3,6].

Although Miranda and colleagues reported the dose of pramipexole could be as high as 0.75 mg per day without adverse effect[7], the safe dose has not yet been fully investigated in uremic patients. Theoretically, a synergic effect between amantadine and pramipexole might amplify the severity of intoxication even though pramipexole is not overdosed. However, literature discussion about this interaction is scarce.

According to previous reports, toxic manifestations in patients with renal failure took place from 3 days to 4 months after administration of amantadine[3,4]. As to our patient, she had taken amantadine 200 mg per day for two weeks. The toxic manifestations include progressive ataxic gait, tremor, myoclonus, and rapid mental change followed by sudden death which is most likely due to amantadine-induced cardiac arrhythmia (we could not obtain the amatadine drug level at that time). However, the synergic effect of amantadine and pramipexole should be considered because theoretically it may contribute to the fatal outcome in our patient. Attention should be paid to the clinical course of toxic encephalopathy: the occurrence of disturbed consciousness may be far behind the appearance of myoclonus and ataxia. The importance of early recognition of disturbed consciousness cannot be over-emphasized as mild confusion may be soon pursued by sudden death. Physicians should consider treating Parkinsonian symptoms or restless leg syndrome in uremic patients with L-dopa as the first consideration because of its effectiveness and safety[8].

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