A case of cibenzoline-induced myasthenia-like syndrome is reported. A 67-year-old woman with renal failure and no previous disorder of neuromuscular junction complained of fatigue during climbing up a flight of stairs and experiencing heavy eyelids after administration of 100 mg/day of cibenzoline. Repetitive nerve stimulation tests revealed decrement at 5-10 Hz. After reduction of the dosage, myasthenia-like signs and symptoms disappeared. The peak cibenzoline concentration was still high even after the dose reduction (666.4 ng/ml). In conclusion, cibenzoline, at a high plasma level, may induce myasthenia-like syndrome without any disorder of the neuromuscular junction.

Key words: renal failure, drug induced, atrial fibrillation

Introduction

Numerous drugs are known to promote disorder of the neuromuscular junction (1). Penicillamine induces myasthenia gravis (MG) by inducing autoimmunity, i.e. the production of anti-acetylcholine receptor (AchR) antibodies (2). Beta-adrenergic blockers also induce myasthenia-like syndrome among patients without MG (1, 3). Many other drugs, such as antiarrhythmic agents and antibiotics, aggravate or unmask MG and other disorders of the neuromuscular junction (1).

Cibenzoline is a new antiarrhythmic agent classified as Class Ia (4). In previous reports, the class Ia antiarrhythmic agents were found to only aggravate or unmask the symptoms of myasthenia gravis (1). In this report, we present the first case of cibenzoline-induced myasthenia-like symptoms in a patient without a known disorder of the neuromuscular junction.

Case Report

A 67-year-old woman was admitted to our hospital because of ptosis and muscle weakness. She had hypertension, diabetes mellitus, and Graves’ disease and has been taking antihypertensive and antithyroid drugs for 20 years. At age 60, she was diagnosed as having an aortic dissection (DeBakey type IIIb). Since then, she has been started on a beta-adrenergic blocker and a calcium channel blocker. At age 64, a small cerebral infarction was found on her right internal capsule. At age 67, her plasma creatinine increased and she was admitted to our hospital because of her uncontrolled hypertension and renal insufficiency.

At the first admission to this hospital in April 1992, she was treated with 80 mg of metoprolol, 40 mg of manidipine, and 500 mg of alpha-methyl dopa, however, her blood pressure was 190/105 mmHg. During the first admission, she experienced an attack of paroxysmal atrial fibrillation with a decrease in blood pressure (110/60 mmHg) and an initial transient attack of cerebral ischemia (left hemiparesis), although she occasionally experienced sudden-onset palpitation. Computer assisted tomography and magnetic resonance imaging did not reveal any new infarctions. Her left hemiparesis disappeared within a day.

To control her paroxysmal atrial fibrillation, we started digoxin and cibenzoline in small doses (digoxin 0.1 mg/day and cibenzoline 100 mg/day) because of her renal insufficiency (the serum creatinine concentration 4.0 mg/dl, creatinine clearance 15 ml/min). Her paroxysmal atrial fibrillation completely disappeared shortly after beginning the antiarrhythmic drugs. Two months after starting the antiarrhythmic drugs, she felt fatigue at climbing up the stairs and her eyelids were heavy. Since the symptoms were considered to be the result of progression of renal failure (serum creatinine concentration 5.8 mg/dl, creatinine clearance 10 ml/min) causing edema in the legs and eyelids, loop diuretics (furosemide 40 mg/day) was given but her symptoms did not improve. After a 5-month-administration of the antiarrhythmic drugs, she was readmitted because of...
ptosis, muscle weakness and to make blood access for hemodialysis.

On the second admission, she had no muscle weakness or other neurological abnormality except the signs of a post cerebral infarction and peripheral neuropathy with absence in ankle jerk. In the evening of the fifth day, however, she experienced heavy eyelids. Neurologically, she had left lateral rectal muscle palsy and bilateral ptosis (Fig. 1). Muscle power of other truncal muscles were within normal limits.

Laboratory examination (Table 1) showed that she had renal failure, anemia, and diabetes mellitus but electrolyte and thyroid functions were normal. Her serum creatinine kinase was within normal value. Electrocardiogram showed widened QRS complex (0.08 second to 0.12 second) and elongated QT time (0.40 second to 0.48 second at the first and second admission, respectively). Anti-AchR antibody could not be detected.

Chest computer assisted tomography did not detect any thymoma. Swelling of the ocular muscle, which would suggest dysthyroid ophthalmoplegia, was not found by magnetic resonance imaging.

On electromyography (EMG), the amplitude of compound muscle action potential (CMAP) induced by single stimulation was within normal limits on the median nerve (12.8 mV) and facial nerve. Repetitive nerve stimulation test with 5 and 10 Hz on muscles orbicularis oculi showed a reproducible decrement of more than 20 percent in amplitude and area of successive 5 responses, while that of the median nerve did not. The repetitive nerve stimulation test with a higher frequency was not performed because CMAP was normal in amplitude, and no increment was found at 10 Hz. Edrophonium test was not performed in order to avoid hypotension-induced cerebral ischemia. In needle EMG, there were no signs of myogenic disorders. In conduction studies, mild peripheral neuropathy, suggesting diabetic neuropathy, was found.

On the 15th day of admission, the interval of cibenzoline administration was changed to 100 mg every other day. Two days decreasing the cibenzoline, her ptosis and muscle weakness were resolved and have not recurred. Repetitive nerve stimulation after 1 month showed no decrement. Her plasma cibenzoline concentration, measured after changing the interval of cibenzoline administration, were 213.6 ng/ml (trough) and 666.4 ng/ml (peak; effective range 277–329 ng/ml).

Six months later, hemodialysis was started and the interval of cibenzoline administration was changed again to 100 mg every 3 days. Her myasthenia-like signs and symptoms and paroxysmal palpitation have not recurred for three years.

**Discussion**

There are many drugs which cause drug-induced myasthenia-like syndrome. Some of them induce myasthenia-like syndrome among patients without myasthenia gravis (MG) due to the immunological (e.g., d-penicillamine) and pharmacological (beta-adrenergic blockers) effects of the drugs. Many other drugs, such as antiarrhythmic agents and antibiotics, aggravate or unmask MG and other disorders of neuromuscular junction (1). In this report, we present a case of cibenzoline-induced myasthenia-like syndrome in a patient without any neuromuscular junction disorders. The beta-adrenergic blocker and calcium channel blocker she has taken are also suspects for the causes of her myasthenia-like symptoms. However, the probability of these agents promoting her myasthenia-like symptoms is quite low, since she has been placed on these drugs years before the onset of symptoms.

Cibenzoline is a new antiarrhythmic drug classified as class Ia, however, this drug also has a lesser extent, class III and IV antiarrhythmic activity (4). Myasthenia-like syndrome induced by antiarrhythmic agents of class Ia (quinidine, procainamide, dysopyramide), class Ib (phenytoin), and class II (beta-adrenergic blockers) have been reported (1). Recently, the class Ic
agent, propafenone (5), and class IV agent, verapamil (6, 7) were also found to induce myasthenia-like syndrome.

Myasthenia gravis is considered to be an autoimmune disease. Antibody-mediated autoimmune attack decreases the number of available acetylcholine receptors at neuromuscular junctions (8). This disease is often associated with thymoma (10%) and detectable anti-AchR antibodies (80%). In our case, neither thymoma nor anti-AchR antibodies could be detected. In addition, the patient has not shown symptoms of MG for 3 years. These results suggest this patient did not have subclinical MG.

The mechanisms of the myasthenia-like syndrome differ among the drugs. For example, beta-adrenergic blockers induce myasthenia-like syndrome even in patients without MG to block the neuromuscular transmission by acting as a local anesthetic at the presynaptic level (1). On the other hand, procainamide has a postsynaptic, receptor-blocking effect. Other drugs (e.g. phenytoin, verapamil) promote the syndrome by a combination of these mechanisms (7).

The repetitive nerve stimulation test manifested the pattern of MG and did not show decrement followed by increment, which is typically seen in the Lambert-Eaton myasthenic syndrome, a prejunctional disorder, although we did not perform the edrophonium test and repetitive stimulation test with higher frequencies (i.e. 20 to 30 Hz). The electrophysiologic study suggested that these myasthenia-like symptoms may be related to the blockade at postsynaptic levels.

After elongating the interval between cibenzoline administrations, no abnormal signs of neuromuscular junction were detected by the repetitive nerve stimulation test. Furthermore, this patient had no motor unit disorders, (e.g. poliomyelitis, amyotrophic lateral sclerosis, myotonia, or dysthyroidal ophthalmoplegia) and has not had such a disease for the past 3 years. Therefore, her myasthenia-like symptoms were not caused by the unmasking of a subclinical neuromuscular junction disorder. It can be said that high levels of cibenzoline may induce myasthenia-like signs and symptoms in patients without any neuromuscular disorder.

Cibenzoline is mainly excreted in the urine unchanged, therefore, the dose should be reduced in patients with renal failure (9). We started this drug at 100/mg every day, however, even after the dose reduction, the peak plasma concentration was high. Although we did not measure the cibenzoline concentration when the myasthenia-like signs and symptoms occurred, it may have been within the toxic levels of this drug. Since cibenzoline has an anti-cholinergic effects like other class Ia drugs (10), toxic level of cibenzoline might contribute to myasthenia-like signs and symptoms through anti-cholinergic effect on neuromuscular junction.

In conclusion, myasthenia-like syndrome may be induced by considerably high concentrations of cibenzoline in patients without neuromuscular disorder.

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References