



## Case Report

## Rhabdomyolysis in a patient taking nebivolol

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$\beta$  Blockers such as propranolol and labetalol are known to induce toxic myopathy because of their partial  $\beta_2$  adrenoceptor agonistic effect. Nebivolol has the highest  $\beta_1$  receptor affinity among  $\beta$  blockers, and it has never been reported to induce rhabdomyolysis until now. We report a patient who developed rhabdomyolysis after changing medication to nebivolol. A 75-year-old woman was admitted to our hospital because of generalized weakness originating 2 weeks before visiting. Approximately 1 month before her admission, her medication was changed from carvedilol 12.5 mg to nebivolol 5 mg. Over this time span, she had no other lifestyle changes causing rhabdomyolysis. Her blood chemistry and whole body bone scan indicated rhabdomyolysis. We considered newly prescribed nebivolol as a causal agent. She was prescribed carvedilol 12.5 mg, which she was previously taking, instead of nebivolol. She was treated by hydration and urine alkalization. She had fully recovered and was discharged.

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## Introduction

There are various causes of rhabdomyolysis. Recently, many medicines and substances, including lipid-lowering drugs (fibrates and statins), alcohol, heroin, cocaine [1], diuretics, antibiotics, and antifungal agents [2], have been reported as causes of rhabdomyolysis.

Among antihypertensive agents, it has been reported that  $\beta$  blockers, such as propranolol [3], labetalol [4], pindolol [5,6], and xamoterol [6], can result in toxic myopathy, which induces muscle cramps, pain, and muscle enzyme elevation.

Nebivolol is a selective  $\beta_1$ -blocker with a nitric oxide–potentiating vasodilatory effect in comparison with other  $\beta$  blockers [7]. Nebivolol has a direct stimulatory effect on

endothelial nitric oxide synthase, which results in increased levels of local nitric oxide [8,9]. It has been reported that nebivolol has an antioxidant effect [7,10]. In addition, there has been no published report of nebivolol-induced rhabdomyolysis. Although it is thought to have a more favorable side effect profile compared to other  $\beta$  blockers [11], nebivolol can possibly induce rhabdomyolysis. We treated a patient who developed rhabdomyolysis induced by nebivolol.

## Case report

A 75-year-old woman was admitted to our hospital because of generalized weakness. The patient had been suffering from generalized weakness and anorexia for 2 weeks and remotely experienced symptom onset 1 month earlier. She had pain on the right knee and right thigh but no respiratory or cardiovascular symptoms suggesting infectious disease such as cough, sputum, rhinorrhea, sore throat, or fever. She had no other lifestyle changes, including trauma history, severe

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exercise, burn, or diet, except for her change in medication from carvedilol 12.5 mg to nebivolol 5 mg 1 month before her admission. She visited a private clinic, and her serum levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were elevated markedly. She was transferred to an emergency room for further evaluation.

Previously, she was diagnosed with hypertension 11 years ago and severe cardiovascular disease (3-vessel disease) treated with a coronary artery bypass graft 4 years ago. She had taken fluvastatin 80 mg, valsartan 80 mg, aspirin 100 mg, and carvedilol 12.5 mg daily for 4 years. One month before her admission, carvedilol was changed to nebivolol 5 mg daily. She did not have diabetes mellitus, chronic hepatic disorder, or chronic kidney disease. She was a housekeeper without a history of smoking, alcohol intake, or herbal medication.

On physical examination, the patient was obese (body mass index, 26.57 kg/m<sup>2</sup>). Initial blood pressure was 136/66 mmHg. The heart rate was 62 beats/min. The respiration rate was 20 breaths/min. Body temperature was 36.7°C. Her mental status was alert, and orientation was intact. She cannot stand up on her own strength because of generalized weakness and right knee pain. Muscle strength was decreased to Grade II on the right lower leg and Grade IV on the other extremities and trunk. No significant tender point was found. Her urine was a dark color when examined in the emergency room.

On the day of admission, her blood test disclosed the following: AST 1,091 IU/L, ALT 913 IU/L, blood urea nitrogen (BUN) 56.8 mg/dL, creatinine 1.3 mg/dL, lactate dehydrogenase (LDH) 6,541 IU/L, creatine kinase (CK) 37,399 U/L, CK-MB 399.7 ng/mL, troponin I 0.15 ng/mL, erythrocyte sedimentation rate 54 mm/h, and C-reactive protein 1.0 mg/dL. The serum

myoglobin level was higher than the upper measurable range (> 3,000 ng/mL).

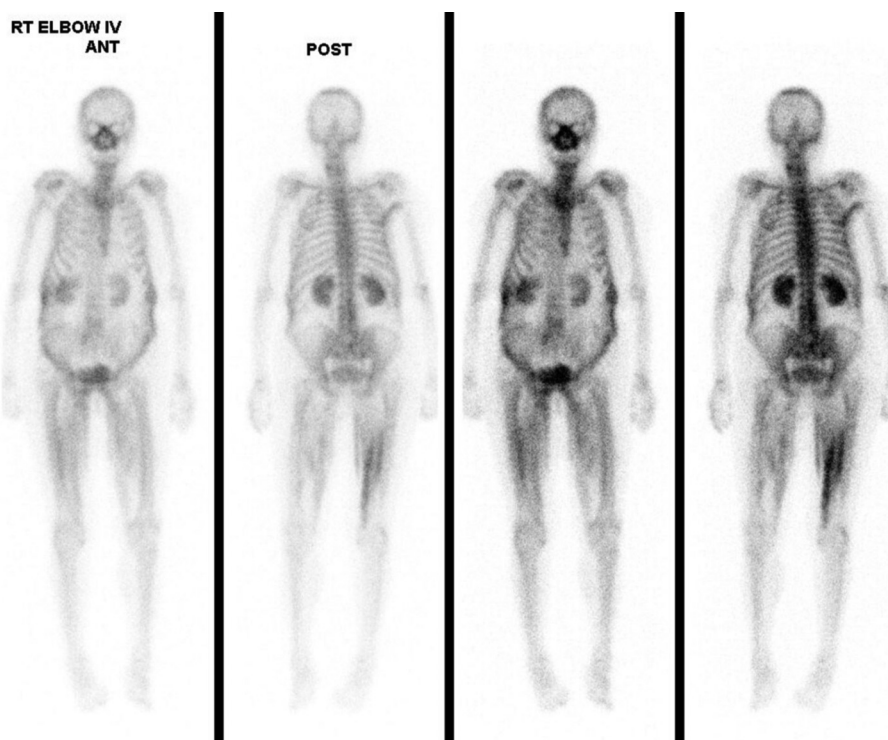
The levels of hemoglobin (13.3 g/dL), platelet (218,000/ $\mu$ L), white blood cells (8,700/ $\mu$ L), total bilirubin (0.7 mg/dL), alkaline phosphatase (106 IU/L), plasma sodium (141 mEq/L), potassium (5.0 mEq/L), chloride (108 mEq/L), phosphorus (4.8 mg/dL), and total calcium (9.4 mg/dL) remained in the normal range. An arterial blood gas analysis at this time revealed a pH of 7.37, PCO<sub>2</sub> 37 mmHg, PO<sub>2</sub> 87 mmHg, HCO<sub>3</sub> 21.4 mmol/L, and O<sub>2</sub> saturation 96%.

The patient had the hepatitis B surface antibody. The results of the test for a hepatitis B surface antigen, hepatitis C antibody, reverse transcriptase-polymerase chain reaction of hepatitis C RNA, human immunodeficiency virus antibody, and rapid plasma reagin were all negative. The test for hepatitis A was not performed in consideration of low incidence of hepatitis A in her age.

The urine was strongly positive (+++) for blood in dipstick test, but only 3–5/hours postfertilization (HPF) red blood cells were present on microscopic examination. Other laboratory results include specific gravity 1.015, pH 5.5, protein (++), glucose (–), ketone (–), bilirubin (–), urobilinogen (trace), nitrite (–), many white blood cells, 2–3/HPF squamous epithelial cells.

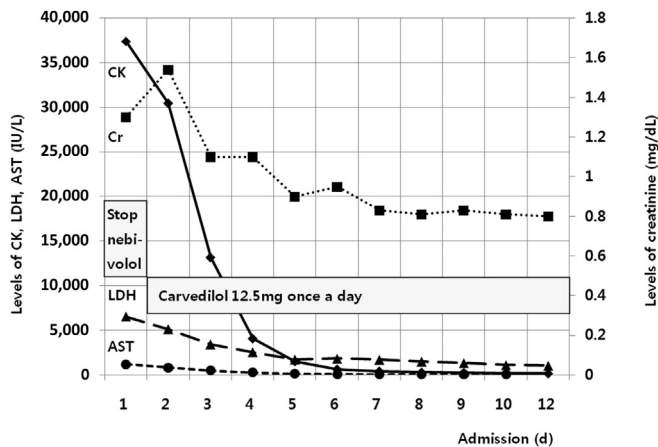
There was no remarkable finding other than a simple cyst on the right kidney on an abdominal ultrasonogram and a cardiac echocardiogram. An electrocardiogram showed sinus rhythm with normal intervals.

Technetium-99m hydroxymethane diphosphonate bone scintigraphy showed increased tracer uptake in the abdominal wall, both thighs, both deltoid muscles, and the right teres muscles (Fig. 1).



**Figure 1. Tc-99m HDP bone scintigraphy.** An increased tracer uptake was shown in the abdominal wall, both thighs, both deltoid muscles, and right teres muscles.

HDP, hydroxymethane diphosphonate.



**Figure 2.** Levels of CK (U/L), LDH (IU/L), AST (IU/L), and Cr (mg/dL) during admission.

AST, aspartate aminotransferase; CK, creatine kinase; Cr, creatinine; LDH, lactate dehydrogenase.

She was thought to have drug-induced rhabdomyolysis arising from newly prescribed nebivolol. Prescription of nebivolol was stopped and changed to carvedilol 12.5 mg/d again. She was admitted and treated by massive hydration and urine alkalization. Altogether, 2 L of 5% dextrose saline solution mixed with sodium bicarbonate (20 mEq/L) was administered. We decided to observe for pyuria.

On the next day, reduction was observed in levels of CK (30,430 IU/L), liver transaminases (AST 778 IU/L and ALT 749 IU/L), and LDH (5,137 IU/L). BUN (1.54 mg/dL) and creatinine (1.54 mg/dL) levels were slightly elevated. On the third admission day, BUN (50.3 mg/dL) and creatinine (1.10 mg/dL) also showed decreases (Fig. 2).

On the sixth day after admission, all the urinalysis results were normal: specific gravity 1.011, pH 5.0, protein (–), erythrocyte (–), 1–2/HPF red blood cells, and 0–1/HPF white blood cells.

On the 10<sup>th</sup> day after admission, the level of AST was decreased to 28 IU/L and ALT to 94 IU/L. On the 12<sup>th</sup> day after admission, her blood chemistry showed creatinine 0.8 mg/dL, CK 138 U/L, and LDH 1,022 IU/L and her generalized weakness had fully recovered.

On the 13<sup>th</sup> day after admission, the patient was discharged. She was prescribed carvedilol 12.5 mg for  $\beta$  blocker, and all other medications were continued as before.

## Discussion

Nowadays,  $\beta$ -adrenergic blocking agents are widely used drugs for patients with various cardiovascular diseases such as hypertension, angina, myocardial infarction, and heart failure [12]. Many combinations of drugs recommended for patients with cardiovascular disorders include  $\beta$  blockers, lipid-lowering agents, antiplatelet agents, and angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers are commonly included among the combinations. It is well known that all the aforementioned drugs have been reported as a cause of myopathy, especially the 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors.

The frequency of statin myopathy (including myalgia, muscle weakness, and elevation of serum CK level) is different

among various studies. Maron et al [13] described that myopathy with statin monotherapy occurs in ~1 of 1,000 patients and is dose related. Ucar et al [14] analyzed the World Health Organization's International Drug Information System database and found myopathy to account for 0.02–1.8% of all adverse reactions associated with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors and rhabdomyolysis to account for 0.2–2.1%.

Rhabdomyolysis is the most serious side effect of statin therapy, in cases where renal insufficiency is already present. However, in some studies, this side effect was found to be rare (affecting 0.1% of statin users) [14,15], and no cases of drug-related rhabdomyolysis were reported in some follow-up studies [16,17]. Antons et al [18] reported that the incidence rate of rhabdomyolysis during statin monotherapy was 0.0042% per 1 year of therapy. Alsheikh-Ali et al [19] demonstrated that a rate of rhabdomyolysis in a high-dose simvastatin (80 mg) trial [20] was more than 7-fold higher than that in intermediate-dose simvastatin (40 mg) trials (67 vs. 9 cases of rhabdomyolysis per 100,000 person-years), but the risk of rhabdomyolysis was not increased in clinical trials of other high-dose statins (lovastatin 80 mg, simvastatin 80 mg, fluvastatin 80 mg, and atorvastatin 80 mg).

When we focused on  $\beta$  blockers, we found that many side effects of  $\beta$  blockers were already reported. Side effects, such as bradycardia, hypotension, orthostatic hypotension, malaise, dizziness, occur commonly in clinical situations. The main side effects of  $\beta$  blockers, such as myocardial depression and hypotension, are caused by their excessive therapeutic effects, leading to tissue hypoperfusion. There are case reports of complications with  $\beta$ -blocker ingestion including mesenteric ischemia [21], acute renal failure [22], and rhabdomyolysis [23].

It was also reported that toxic myopathy resulted from  $\beta$  blockers such as propranolol, labetalol, pindolol, and xamoterol [3–6]. The rise in the CK level or muscle cramps occur more frequently with pindolol than propranolol and may be related to the partial  $\beta$ -adrenergic receptor agonist activity. Mechanism of this elevation of CK with pindolol is unclear but appears to be due to increased permeability of the cell membrane and the density and reactivity of the  $\beta_2$  adrenoceptors on the membrane [6]. Skeletal muscle contains a significant proportion of  $\beta_2$  adrenoceptors, but there are also 7–10% of  $\beta_1$  adrenoceptors and a smaller proportion of  $\alpha$  adrenoceptors [24]. Some  $\beta_2$  agonists could increase skeletal muscle mass by regulation of protein synthesis, gene transcription, and apoptosis [24], but pure  $\beta_2$  agonists may cause muscle cramps [25]. Xamoterol is a selective  $\beta_1$  adrenoceptor agonist, which has stimulatory effect on sinoatrial and atrioventricular nodes of the heart. The absence of any rise in CK levels during treatment with or after withdrawal of xamoterol would suggest that the CK response may be due to specific  $\beta_2$  adrenoceptor partial agonism [6].

Generally, nebivolol is thought to have a more favorable side effect profile than other  $\beta$  blockers. Van Bortel et al [11] demonstrated that tolerability between nebivolol and angiotensin-converting enzyme inhibitors was similar, but nebivolol had better tolerability than other  $\beta$  blockers, calcium channel antagonists, and the angiotensin II receptor antagonists, including losartan, by analyzing data from 8 studies comparing nebivolol with other antihypertensive drugs. In a meta-analysis of 10 trials comparing nebivolol with atenolol, bisoprolol, and metoprolol, nebivolol showed few adverse events and drug withdrawals while exhibiting similar efficacy [26].

Rhabdomyolysis occurred while taking nebivolol, whereas it did not occur while taking carvedilol in this patient. Although the mechanism responsible for nebivolol-induced rhabdomyolysis is unclear, there are several reported differences between nebivolol and carvedilol that are useful to estimate the possible causes.

Carvedilol is a comprehensive  $\beta$  blocker that blocks  $\beta_1$ ,  $\beta_2$ , and  $\alpha$  receptors in the heart [27].  $\beta_1$ -selective  $\beta$  blockers upregulate  $\beta_1$  receptor density and increase  $\beta_1$  receptor sensitivity to adrenergic stimulation; this has not been seen with carvedilol [28].

Nebivolol has the highest  $\beta_1$  receptor affinity among  $\beta$  blockers, and  $\alpha$ -blocking properties, and agonistic activity on  $\beta_3$  receptors [8]. It also has vasodilating properties attributed to its interaction with the L-arginine nitric oxide pathway, a property not shared by other  $\beta$  blockers [29]. That is the reason why nebivolol led to a greater reduction of diastolic blood pressure than carvedilol although they demonstrated similar efficacy on systolic blood pressure reduction [30]. Produced via 2-step oxidation of L-arginine, nitric oxide has potent antiatherosclerotic properties and inhibitory effect on the proliferation of smooth muscle cells in high concentrations [8].

There is a possibility that rhabdomyolysis was induced by the agonistic activity on  $\beta_3$  receptors of nebivolol. Sprague et al [31,32] demonstrated that carvedilol reverses hyperthermia and subsequent rhabdomyolysis induced by 3,4-methylenedioxy-methamphetamine (MDMA, ecstasy) in an animal model. MDMA-induced hyperthermia is commonly associated with skeletal muscle breakdown, rhabdomyolysis, and renal failure. The mechanism of MDMA-induced hyperthermia is considered to be a combination of the following:  $\alpha$ -1 adrenoceptor activation resulting in thermogenesis and visceral vasoconstriction to divert blood to skeletal muscle,  $\beta_3$  adrenoceptor activation resulting in skeletal muscle thermogenesis, and activation of the skeletal muscle thermogenic protein, uncoupling protein-3. Carvedilol blocks these receptors so that it attenuates MDMA-induced CK release.

As far as we know, this is the first published case of nebivolol-induced rhabdomyolysis. In previously reported cases of rhabdomyolysis, there is only one patient who was indicated to have been taking a combination of drugs including nebivolol. Medications other than nebivolol were thought to be the causative agent in these cases [33].

Our case report shows the possibility of myotoxicity with nebivolol. The patient had taken carvedilol as a  $\beta$  blocker for 56 months and fluvastatin for 32 months, but her symptom occurred about 2 weeks after changing medication from carvedilol to nebivolol. Furthermore, she had completely recovered after hydration and restoring her medication to carvedilol. Moreover, the patient remained free from other complications of drugs, such as myopathy, for 9 months through to her most recent follow-up. These sequential events are enough to arouse suspicion that nebivolol has a causal relationship with rhabdomyolysis.

The amount of creatinine elevation (up to 1.5 mg/dL) was mild although the level of CK (37,399 U/L), AST (1,091 IU/L), and ALT (913 IU/L) was highly elevated in this case. We were unable to analyze a clinical difference between this case and other case reports of  $\beta$  blocker-induced rhabdomyolysis in detail because of the small number of cases.

Looking back in the case of this patient, we should also consider the possibility that rhabdomyolysis was induced by

the interaction of nebivolol and other previously administered drugs such as fluvastatin. Omar et al [34] found that statin drugs alone or in combination therapy can cause rhabdomyolysis. Wagner et al [35] conducted an *in vitro* study and reported that combination treatment with propranolol and statins causes additive muscle toxicity in a dose-dependent manner, but the cohort study conducted by Setoguchi et al [3] found no evidence of a synergistic effect between the use of propranolol and statins in causing myopathy.

The patient was admitted in February which was the flu season, so we should also consider the possibility of infection-induced rhabdomyolysis in addition to medication. The most common viral etiology of rhabdomyolysis is influenza virus, followed by human immunodeficiency virus, Coxsackie virus, and Epstein-Barr virus, and the most common bacterial organisms are *Legionella* species, followed by *Francisella tularensis*, *Streptococcus* species, and *Salmonella* species [36]. The patient did not present any symptoms or signs to suspect an infection such as fever, chills, sore throat, cough, sputum, rhinorrhea, diarrhea, or abdominal pain. Therefore it was considered that there was no need for additional tests to rule out other respiratory or gastrointestinal infection.

Her technetium-99m hydroxymethane diphosphonate bone scintigraphy showed increased tracer uptake not only in the weakened right thigh but also the muscles of the trunk, which had no remarkable symptom. Soft tissue uptake at bone scintigraphy can be found because of benign (myositis ossificans and tumoral calcinosis) and malignant (osteogenic sarcomas and adenocarcinomas) calcification, inflammation (polymyositis and soft tissue infection), and increased physical exercise [37-40]. There was no extrasosseous calcification on her chest X-ray examination and no leukocytosis, focal erythema, or tenderness suggesting inflammation. She recovered only with massive hydration without administration of antibiotics or immunosuppressants, and her muscle weakness has not recurred in the 17-month follow-up period. It is suspected that the cause of the increased tracer uptake in the trunk is the increased use of muscles of the trunk and upper extremity due to the weakness in the right leg or personal habits of the patient.

In summary, nebivolol, a third-generation  $\beta$  blocker, has been in the limelight as a relatively safe antihypertensive agent so far, but there is a possibility of it causing rhabdomyolysis when taken alone or in combination with other agents. Therefore, when a patient taking nebivolol is suspected to be affected by myopathy or rhabdomyolysis, nebivolol should be considered as a potential culprit and be discontinued if possible.

## Conflicts of interest

All authors have no conflicts of interest to declare.

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