

## Gabapentin-Induced Rhabdomyolysis in a Patient with Diabetic Neuropathy

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### Abstract

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Gabapentin (GBP) is a drug which is frequently used in diabetic neuropathy. Common adverse effects of GBP include drowsiness, dizziness, ataxia, somnolence, and fatigue. Rhabdomyolysis is an extremely rare side effect of GBP. In this report we describe a case of GBP-induced rhabdomyolysis in a 63-year-old diabetic woman. She presented with severe muscle pain in her extremities, fatigue, decreased urine output and urine discoloration within 3 weeks after starting treatment with GBP (900 mg/day) for diabetic neuropathy. Laboratory tests revealed extreme elevations of muscle enzymes, increased creatinine and potassium levels. She required hemodialysis as a result of anuria. Investigation confirmed the diagnosis of rhabdomyolysis, and discontinuation of GBP resulted in resolution of clinical and biochemical features of rhabdomyolysis.

**Key words:** Gabapentin, rhabdomyolysis, diabetic neuropathy

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### Introduction

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Diabetic neuropathy is a common complication of diabetes mellitus (DM) and occurs in approximately 50% of diabetic patients over time (1). Gabapentin (GBP), an anticonvulsant, has been shown to be efficacious in the treatment of painful diabetic neuropathy (PDN) (2). The most frequent side effects (>10%) of GBP include somnolence, dizziness, ataxia, and fatigue. Other side effects are nystagmus, headache, tremor, diplopia and nausea, each occurring in less than 10% of patients (3). In recent years, two reports have suggested that GBP may be associated with myopathy (4, 5). In this report, we describe a case of rhabdomyolysis and myoglobinuria complicated by acute renal failure following the use of GBP in a patient with PDN.

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### Case Report

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A 63-year-old woman presented with fatigue, gait instability, diffuse muscle pain, and muscle weakness in her lower extremities. These symptoms started approximately 2

weeks prior to her presentation and rapidly progressed over the previous 3 days. The patient also noted decreased urine output with a reddish color in the past two days. She denied any previous infection or trauma. Past medical history revealed type 2 DM for 10 years, hypertension for 5 years, and dyslipidemia for a year. At the time of admission she was on multiple daily insulin injections (nearly 2 years), irbesartan (150 mg/day; nearly 1.5 years), and GBP (900 mg/day). Three weeks prior to presentation she went to an outpatient clinic for routine health maintenance, and GBP (300 mg, three times a day) was prescribed for PDN. At that time her laboratory tests were as follows: urea: 38 mg/dL, creatinine: 1.2 mg/dL, estimated glomerular filtration rate (GFR): 48 mL/min/1.73 m<sup>2</sup>, creatine phosphokinase (CPK): 142 U/L, aspartate aminotransferase (AST): 26 U/L, HbA1c: 7.2%, and microalbuminuria: 170 mg/24 h. There was no evidence of diabetic retinopathy.

On admission, physical examination revealed proximal muscle tenderness on upper and lower extremities, and proximal muscle weakness (3/5) in both legs. The ankle jerk reflexes were both absent and vibration sensation was decreased in both feet. Laboratory studies disclosed acute renal

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**Table 1.** Laboratory Results of the Patient

Parameter	Before GBP treatment	Days during hospital follow-up										6 months after discharge
		1	3	5	8	10	12	15	18	20		
CPK (26-167 U/L)	142	75680	43400	9248	6689	2640	1262	884	857	323	136	
CK-MB (0-25 U/L)		680	416	193	84	70	57	52	42	39		
AST (1-32 U/L)	26	1451	1090	503	405	197	121	118	102	80	41	
ALT (7-35 U/L)	21	453	393	267	252	172	141	132	116	73	26	
Myoglobin (<60 ng/mL)					1392			135				
Myoglobinuria (ng/mL)					1384			121				
Urea (10-50 mg/dL)	38	278	256	235	213	189	186	184	143	67	41	
Creatinine (0.6-1.3 mg/dL)	1.2	7.9	6.9	6	5.6	5.1	4.4	4	3.1	2.7	1.1	
Potassium (3.5-5.2 mmol/L)		6.3	5	4.6	4	4.3	3.8	3.7	3.6	3.5		

CPK= creatine phosphokinase; AST= aspartate aminotransferase; ALT= alanine aminotransferase

failure with a creatinine level of 7.9 mg/dL, a CPK level of 75,680 U/L (26-167 U/L), AST level of 1,451 U/L (1-32 U/L), lactate dehydrogenase (LDH) level of 1,847 U/L (240-480 U/L) and potassium level of 6.3 mmol/L (3.5-5.5 mmol/L). Thyroid hormones and troponin-I were within the normal range. The urine was positive for myoglobin. Electromyogram demonstrated myopathic motor unit potentials with frequent fibrillations and positive sharp waves, and asymmetrical sensorimotor polyneuropathy with mixed axonal and demyelinating features. The patient underwent emergent hemodialysis for elevated potassium levels and anuria. Muscle biopsy showed changes indicative of myopathy, and the patient was diagnosed with rhabdomyolysis. GBP was stopped, and parenteral fluids were carefully given with furosemide to induce diuresis. Her symptoms gradually ceased with steady improvement of renal function and a decrease in CPK levels (Table 1). She continued with hemodialysis and was discharged 20 days after initial presentation. At a 6-month follow-up, she was asymptomatic with normal renal function and muscle enzymes.

## Discussion

In this report we presented a case of rhabdomyolysis complicated by acute renal failure in a patient receiving GBP for PDN. Gabapentin was thought to be the causal agent based on the following factors: the temporal relationship between the onset of symptoms, which occurred one week after the introduction of the drug; the clinical and biochemical resolution, which occurred after discontinuation of the drug; the absence of an alternative explanation for the rhabdomyolysis, as there was no trauma, signs of infection, thyroid dysfunction, or additional new medications. In addition,

the Naranjo probability scale (6) indicated a probable (8 points) relationship between rhabdomyolysis and GBP therapy.

Rhabdomyolysis is a condition characterized by muscle necrosis resulting in the release of muscle cell contents into the systemic circulation. The classic triad of signs includes muscle injury, pigmented urine due to myoglobinuria, and renal dysfunction. The severity of illness ranges from asymptomatic elevations in serum muscle enzymes to life-threatening cases associated with extreme enzyme elevations, electrolyte imbalances, and acute renal failure (7, 8).

Rhabdomyolysis has many etiologies. Among the most common are trauma, intense exercise, infection, drugs, and toxins. Exposure to toxic agents, including alcohol and medications, accounts for up to 80% of rhabdomyolysis cases in adults (7, 8). Several drugs, including statins, fibrates, neuroleptics, colchicine and proton pump inhibitors may cause rhabdomyolysis (7-10). In the literature, to the best of our knowledge, there are two case reports with respect to GBP use and myopathy (4, 5). Tuccori et al (5) reported an 85-year-old insulin-dependent diabetic woman who developed myopathy and renal impairment after GBP administration (450 mg/day). In that case, on the 7th day of GBP treatment, CPK increased to a level of 3,095 U/L, and creatinine increased to a level of 4.77 mg/dL. Discontinuing GBP resulted in a prompt improvement in her symptoms and muscle enzymes. CPK and creatinine returned to normal after 10 days. She did not require hemodialysis during this period. Although her symptoms and laboratory findings improved after the cessation of GBP, she died from sudden respiratory failure (5). Lipson et al (4) reported two cases of myopathy in patients receiving hemodialysis. GBP was administered for restless leg syndrome and at a dose of 100

mg/day. One of the patients (52-year-old man) reported numbness in his lower extremities and arms nearly one month after GBP treatment. His CPK level increased to 1,031 U/L, and cessation of GBP was associated with a rapid improvement in his symptoms. Two months after stopping the GBP treatment, CPK concentrations normalized. The other case (43-year-old man), presented with numbness of the lips, and his symptoms started nearly one month after GBP administration. CPK increased to 814 U/L and his symptoms resolved within 1 week after discontinuing GBP. CPK levels normalized 3 weeks after stopping treatment (4).

Gabapentin is not metabolized, and is excreted solely by kidney. For that reason GBP dose must be reduced for patients with renal insufficiency (11, 12). In literature, published cases of GBP related adverse events including rhabdomyolysis occurred mostly in the setting of either acute or chronic renal dysfunction (4, 5, 13-15). Our case also had moderate renal dysfunction (GFR: 48 mL/min/1.73m<sup>2</sup>) be-

fore GBP treatment and the administered dose was 900 mg/d (300 mg, three times a day). This dose seems appropriate according to the manufacturer's recommendations (200-700 mg twice/day; GFR=30-59 mL/minute) (11, 12), but we cannot exclude the possibility of toxic blood levels resulting from the accumulation of the drug which may have contributed to the development of rhabdomyolysis.

The mechanism of GBP-induced myopathy is not known. However, GBP may act on voltage-gated calcium and sodium channels in muscle cells and may cause alterations in the intracellular calcium/sodium balance to promote the onset of myopathy (5, 16, 17).

In conclusion, GBP may be associated with rhabdomyolysis and it should be considered in the differential diagnosis of drug induced rhabdomyolysis. Appropriate dosing adjustments and close laboratory follow-up should be made in patients receiving GBP in case of renal insufficiency.

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