

CASE REPORTS

Gabapentin-Induced Neurologic Toxicities

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Gabapentin is an antiepileptic drug approved for the treatment of postherpetic neuralgia and as adjunctive therapy for partial seizures. The drug has been shown to be safe and nontoxic. The current literature has limited reports of neurologic toxicity associated with gabapentin therapy in patients with or without renal dysfunction. We describe the case of a 75-year-old man with renal dysfunction who developed neurologic toxicity due to gabapentin accumulation. Future studies are warranted to confirm the neurologic adverse effects of gabapentin, including any additional risks in patients with renal dysfunction.

Key Words: Neurontin, gabapentin, myoclonus, asterixis, renal failure, neurologic toxicity, adverse effects.

(*Pharmacotherapy* 2005;25(12):1817–1819)

Gabapentin was approved by the United States Food and Drug Administration for the treatment of postherpetic neuralgia and as adjunctive therapy for partial seizure disorders.¹ The mechanism of action regarding gabapentin's analgesic activity is not well understood, and absorption is not dose dependent. Gabapentin is a relatively safe and tolerable drug with only minimal adverse effects, such as somnolence, dizziness, and peripheral edema.^{1,2} Reports of rare adverse effects including painful gynecostasia and hypoglycemia, as well as neurologic abnormalities, have been published.^{3–6} The data, however, are lacking regarding the neurologic toxicity of gabapentin in patients with renal dysfunction. We describe the case of a patient with renal dysfunction who was taking gabapentin for postherpetic neuralgia and developed neurologic toxicities.

Case Report

A 75-year-old man was admitted to the hospital with a chief complaint of weakness and muscle

spasms for 3 days; he had fallen twice during a 1-week period due to myoclonic episodes. His medical history consisted of coronary artery disease, two myocardial infarctions, a coronary artery bypass graft, chronic heart failure, carpal tunnel syndrome, and stage IV chronic lymphocytic leukemia. Before admission, his drug therapy consisted of furosemide, carvedilol, ramipril, aspirin, acyclovir, and gabapentin. The patient also admitted to increasing his diuretic dosage (without his physician's approval) just before admission.

On admission, the patient was alert and not in any acute distress. His height was 5 ft 10 in. and he weighed 84 kg. Physical examination revealed hypotension with a blood pressure of 82/36 mm Hg, jugular vein distention of 6–9 mm, benign abdomen, dry mucous membranes, and decreased sensation in the extremities. On the morning of hospital day 1, several laboratory results were significant, including a white blood cell count of $18.7 \times 10^3/\text{mm}^3$ (normal range $3.4\text{--}10 \times 10^3/\text{mm}^3$), hemoglobin level 9.5 g/dl (13.6–17.5 g/dl), hematocrit 27% (41–53%), and platelet count $87 \times 10^3/\text{mm}^3$ (140–450 $\times 10^3/\text{mm}^3$). Abnormal electrolyte values were sodium 130 mEq/L (134–143 mEq/L), potassium 5.3 mEq/L (3.4–4.9 mEq/L), blood urea nitrogen 74 mg/dl (8–23 mg/dl), phosphate 6.5 mg/dl (2.4–4.6 mg/dl), and creatinine clearance 26 ml/minute. The patient developed a fever, with

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laboratory results indicating an increase in white blood cell count to $33 \times 10^3/\text{mm}^3$, along with a uric acid level of 16 mg/dl (3.7–7.7 mg/dl) and a lactate dehydrogenase level of 283 IU/L (91–185 IU/L). A diagnosis of acute renal failure due to acute tumor lysis syndrome was made.

Before admission, the patient had been receiving gabapentin 800 mg 4 times/day for postherpetic neuralgia. During the morning of hospital day 1, however, the first dose of gabapentin was given, but the remaining doses were held because of unresolved acute renal failure. Gentle fluid repletion with half normal saline at 75 ml/hour had been started the night before, on admission. Other drug therapies begun on admission were albuterol and pantoprazole; aspirin, acyclovir, and carvedilol were continued.

During the afternoon of hospital day 1, the patient was transported to abdominal ultrasonography. During the procedure, however, he experienced multiple episodes of mental status changes, severe asterixis, and episodes of multifocal myoclonus. The patient's symptoms resolved with supportive care, specifically fluid repletion. On hospital day 2, the patient's mental status was improved, electrolyte levels were normal, and creatinine clearance stabilized at 67 ml/minute. Gabapentin was restarted at 300 mg 3 times/day along with the drugs already scheduled. The patient did not manifest signs of altered mental status or neurologic adverse effects when gabapentin was restarted. On the afternoon of hospital day 2, the patient continued to be stable without symptoms of toxicity. He was transferred to the hematology-oncology service for evaluation of his chronic lymphocytic leukemia.

Discussion

Gabapentin is described as a structural analog to the neurotransmitter γ -aminobutyric acid (GABA). One author proposed that gabapentin stimulates the release of GABA, but to date the exact mechanism of action is unknown.⁷ Gabapentin is similar to other antiepileptic drugs such as carbamazepine and valproic acid, both of which enhance GABAergic transmission. The same author also proposed that the increased release of neurotransmitters in the brain produces neurologic toxicity, causing myoclonus and dystonic reactions.⁷

In our patient, the adverse reaction was likely the result of a drug-induced event caused by gabapentin since the drug can cross the blood-

brain barrier and affect neurologic transmission, in contrast to the other drugs that the patient was receiving. Gabapentin is not metabolized and is solely dependent on renal excretion for removal from the body. In fact, gabapentin clearance is linearly proportional to creatinine clearance. The half-life of gabapentin is 5–7 hours with normal renal function, but when renal function is impaired or when renal failure occurs, the half-life can range from 52–132 hours.⁸ Our patient was an elderly man who experienced acute renal failure of unknown duration, therefore increasing his risk for gabapentin accumulation and adverse effects. In the limited literature available, we did find reports describing neurologic toxicities in patients with renal dysfunction who were taking gabapentin.

Three case reports outlined the risks and neurologic toxicities associated with gabapentin. The first case report described a patient experiencing disabling asterixis with normal renal function who was taking gabapentin 3600 mg/day.⁹ Asterixis is a myoclonic reaction that gives rise to sudden movements and a loss of posture. The most common causes for asterixis are metabolic abnormalities, encephalopathy, and drug-induced reactions including those due to antiepileptic drugs. The adverse effects experienced by the patient subsided on discontinuation of gabapentin.

A second case report described a patient taking gabapentin 900 mg/day for postherpetic neuralgia.¹⁰ The patient developed asterixis on the fourth day of therapy. The patient's electrolyte levels and thyroid and kidney function were normal. The drug was discontinued, and symptoms subsided. The patient was rechallenged at a lower dosage of 300 mg/day, without recurrence.

Myoclonus was assessed in patients receiving gabapentin; 13 cases of myoclonic episodes were found, and almost half of the patients experienced altered mental status.¹¹ Dosages ranged from 800–3200 mg/day, with an average daily dose of 2000 mg. In those patients who discontinued gabapentin, the myoclonic episodes resolved.

After reviewing these case reports, we hypothesized that high doses of gabapentin may induce neurologic adverse effects in patients without impaired renal function. In patients with reduced renal function, the risk for neurologic toxicities may be increased due to gabapentin pharmacokinetics as well as unknown pharmacodynamic factors.

Although myoclonus and asterixis have developed in patients with normal renal function who are taking high doses of gabapentin, studies outlining the effects of gabapentin toxicity in patients with impaired renal function show little difference between small and large doses. The neurologic risks associated with gabapentin toxicity in a patient with impaired renal function need to be assessed. In one study, gabapentin 1800 mg/day produced a mild resting tremor and a decrease in cognitive function.¹² The patient was undergoing hemodialysis and was found to have a high serum gabapentin concentration of 85 µg/ml (reference range 2–15 µg/ml). The dose was reduced to 600 mg after hemodialysis, but the symptoms persisted. Another study using a pharmacokinetic analysis showed that a 300-mg dose of gabapentin in a patient with impaired renal function led to drug accumulation, producing neurologic adverse effects.¹³ In another report, a woman with end-stage renal disease was administered unknown doses of gabapentin without scheduled hemodialysis, which produced a slightly above-normal serum gabapentin level of 22 µg/ml.¹⁴ The patient became tremulous and hyperreflexic, and experienced mental status changes. The patient began hemodialysis, which resolved the adverse effects. On rechallenge, the patient returned 3 months later with similar symptoms due to administration of two extra doses of gabapentin. After discontinuing gabapentin and performing hemodialysis for a second time, the adverse effects improved. Patients with renal dysfunction who experience neurologic adverse effects from gabapentin may be subjected to additional risks, possibly the result of limited drug clearance or due to patient-specific factors.

Conclusion

Gabapentin adverse effects are rare and unlikely in most patients with normal renal function, but the risk of gabapentin neurologic toxicity unrelated to dose may be increased

under conditions of renal dysfunction. Our case suggests the possibility of gabapentin toxicity with adverse effects, including myoclonus, altered mental status, ataxia, and tremors, in patients with acute renal dysfunction. Of the studies assessed, the value of monitoring serum levels of gabapentin has not been validated, and an association among clinical symptoms, dose ranges, and serum levels may be arbitrary. Studies should be conducted to confirm the risk of gabapentin toxicity including neurologic adverse effects, any increased risks associated with renal dysfunction, and the proper laboratory monitoring parameters to consider.

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