

A case of gait disturbance caused by low-dose gabapentin

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Abstract: Gabapentin, an anticonvulsant agent, is now often used for the treatment of neuropathic pain all over the world. It is unclear whether the combined use of gabapentin, sodium valproate, and flunitrazepam results in enhancement of the side effect, a gait disturbance. A 60-year-old man was taking oral sodium valproate for symptomatic epilepsy after a brain contusion and flunitrazepam to relieve insomnia. Oral gabapentin therapy was started for suspected neuropathic pain. Although the initial dose of oral gabapentin (200 mg) relieved the pain, the lower extremities became weak, resulting in a gait disturbance. The therapy was restarted with a halved dose, and this resolved the gait disturbance and relieved the pain.

Keywords: gabapentin, gait disturbance, side effect, neuropathic pain

Introduction

Gabapentin is an antiepileptic drug that likely exerts its effects through selective interactions with the $\alpha 2 \delta$ subunit of voltage-dependent calcium channels.¹ Gabapentin provides effective relief from chronic pain states, such as diabetic neuropathy,² postherpetic neuralgia, and other neuropathic pain states.^{3,4} The major side effects of this analgesic agent include drowsiness, dizziness, and headache.

Gabapentin displays dose-dependent, saturable absorption. The mechanism underlying the absorption pattern is believed to include an active transport process. Combined use of gabapentin with other antiepileptic drugs generally results in synergistic interactions in animal studies.⁵ Whether the combined use of low-dose gabapentin, sodium valproate, and flunitrazepam results in enhancement of the side effects, especially gait disturbances, however, is unknown.

Gait disturbance is a rare side effect of gabapentin, especially at low doses. Gait disturbances occurring during the administration of gabapentin and other antiepileptic drugs have not been reported. We report a case of gait disturbance caused by the combined use of low-dose gabapentin administered for neuropathic pain in the right lower extremity with sodium valproate and flunitrazepam.

Case report

A 60-year-old man was taking oral sodium valproate (1,200 mg/d) that was prescribed to treat muscle weakness, mild pain, paralysis in the upper and lower extremities, and symptomatic epilepsy after a brain contusion caused by a traffic accident 30 years ago. Written informed consent was obtained from the patient. The Asahikawa Medical University ethics committee did not require ethical approval as the medications in the present case were not interventional. The serum concentration of sodium valproate

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Table 1 Time frame of patient background and therapeutic process

Time	Occurrence	Prescribed medication
30 years ago	Muscle weakness, mild pain, paralysis in the upper and lower extremities, and symptomatic epilepsy after a brain contusion.	Sodium valproate 1,200 mg Loxoprofen 180 mg
July 2008	Worsening pain in the right lower extremity.	Flunitrazepam 0.5 mg Sodium valproate 1,200 mg Loxoprofen 180 mg
October 21, 2008	Oral gabapentin was initiated. Initial dose of oral gabapentin (200 mg) resulted in a gait disturbance. Gabapentin was stopped when the gait disturbance appeared.	Flunitrazepam 0.5 mg Sodium valproate 1,200 mg Loxoprofen 180 mg
October 25, 2008	Readministration of gabapentin (200 mg) led to gait disturbances, and the patient visited the emergency room.	Flunitrazepam 0.5 mg Gabapentin 400 mg Sodium valproate 1,200 mg Loxoprofen 180 mg
October 27, 2008	Administration of a halved dose of gabapentin resolved the gait disturbance while providing pain relief.	Flunitrazepam 0.5 mg Gabapentin 400 mg Sodium valproate 1,200 mg Loxoprofen 180 mg

was 29.06 µg/mL. Oral flunitrazepam was administered before bedtime to relieve insomnia. He was not taking any other medications.

He had worsening pain in the right lower extremity for 4 months and was referred to the neurosurgery department of our hospital. The initial examination confirmed muscle weakness in the upper and lower extremities, but both movement and sensation were preserved. Deep tendon reflexes were also normal. Oral gabapentin therapy (400 mg/d; twice daily, 200 mg in the morning and 200 mg in the late afternoon) was started for suspected neuropathic pain.

Although the initial dose of oral gabapentin (200 mg) relieved the pain, the lower extremities became weak, resulting in a gait disturbance. The patient ceased gabapentin therapy, which rapidly alleviated the gait disturbance. Readministration of gabapentin (200 mg) after 4 days caused a gait disturbance, prompting the patient to visit our emergency outpatient unit. His only complaint was gait disturbance due to weakness of the lower extremities. Obvious weakness of the upper extremities, motor impairment, respiratory depression, headache, and dizziness were absent. Oral gabapentin therapy was temporarily ceased, as it was the most likely cause of the gait disturbance. The therapy was restarted with a halved dose (200 mg/d; twice daily, 100 mg in the morning and 100 mg late afternoon), and this resolved the gait disturbance and relieved the pain. Pain relief without a gait disturbance has been achieved by lower dose therapy with oral gabapentin (200 mg/d). The oral administration of sodium valproate was also continued for a period of pain relief therapy. The time frame of patient background and therapeutic process is given in Table 1.

Discussion

The major side effects of gabapentin are drowsiness, dizziness, peripheral edema, vomiting, nausea, and headache. Moore et al⁶ reported that gait disturbances occur in 8.8% of neuropathic pain patients on gabapentin at doses of $\geq 1,200$ mg daily.⁷ In this case, a dose of only 200 mg of gabapentin caused gait disturbances in a patient with neuropathic pain in the right lower extremity. To our knowledge, gait disturbances are a very rare adverse effect of low-dose gabapentin.

Gabapentin has additive effects when administered in combination with certain classical anticonvulsants, including diazepam and valproate.^{8,9} Borowicz et al⁵ reported that gabapentin appears to act synergistically with anticonvulsants, including valproate, based on isobolographic analysis. Several studies report that combined use of gabapentin and benzodiazepine enhances the effects of medications used to treat alcoholism.^{10–12} Based on the abovementioned reports, in the present case, the effects of low-dose gabapentin were enhanced by sodium valproate and flunitrazepam, leading to gait disturbances, despite the low dose of gabapentin. Hepner and Claxton¹³ warned that combined use of gabapentin and anticonvulsants for pain therapy could worsen the side effects of these drugs.

Gabapentin is not metabolized, is not bound to plasma proteins, and is entirely excreted unchanged through the kidney. The elimination half-life is 5–7 hours in healthy subjects. Gidal et al¹⁴ reported that the bioavailability of oral gabapentin is 49%, but this may vary greatly among subjects (5%–74%). Johannessen Landmark et al¹⁵ reported that the

concentration/dose ratio is higher in elderly people than in younger patients and a large number of patients (87%) have serum concentrations below the lower limit of the proposed reference range. In other words, the clinical recommended dose of gabapentin is likely to result in quite different plasma concentrations among patients. In this present case, the serum concentration of gabapentin may have been much higher than the expected concentration. This could be the reason for the gait disturbance despite the recommended low initial dose of gabapentin.

As mentioned earlier, the optimum gabapentin dose for pain relief varies among individuals. Therefore, it is likely that the recommended initial dose was excessive for this particular patient. Scheschonka and Beuche¹⁶ reported similar aggravation of muscle weakness after several days of gabapentin therapy and the condition was resolved after withholding therapy in a female myasthenia gravis patient with neuropathic pain caused by herpes zoster. The patient in the present case had existing muscle weakness in the upper and lower extremities due to a brain contusion, suggesting that the muscle-weakening effect of gabapentin may be prominent in patients with underlying diseases that cause muscle weakening. The underlying diseases in individual patients should be considered when determining gabapentin doses.

The gait disturbance demonstrated in this case was a rare complication of gabapentin therapy, and the detailed mechanism remains unclear. The dose and dosing instructions of gabapentin should be individualized for each patient to ensure safe and effective treatment of neuropathic pain, especially when used in combination with other anticonvulsants.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Field MJ, Hughes J, Singh L. Further evidence for the role of the alpha(2)delta subunit of voltage dependent calcium channels in models of neuropathic pain. *Br J Pharmacol*. 2000;131(2):282–286.

2. Backonja M, Beydoun A, Edwards KR, et al. Gabapentin for the symptomatic treatment of painful neuropathy in patients with diabetes mellitus: a randomized controlled trial. *JAMA*. 1998;280(21):1831–1836.
3. Rowbotham M, Harden N, Stacey B, Bernstein P, Magnus-Miller L. Gabapentin for the treatment of postherpetic neuralgia: a randomized controlled trial. *JAMA*. 1998;280(21):1837–1842.
4. Hahn K, Arendt G, Braun JS, et al. A placebo-controlled trial of gabapentin for painful HIV-associated sensory neuropathies. *J Neurol*. 2004;251(10):1260–1266.
5. Borowicz KK, Swiader M, Luszczki J, Czuczwar SJ. Effect of gabapentin on the anticonvulsant activity of antiepileptic drugs against electroconvulsions in mice: an isobolographic analysis. *Epilepsia*. 2002;43(9):956–963.
6. Moore RA, Wiffen PJ, Derry S, McQuay HJ. Gabapentin for chronic neuropathic pain and fibromyalgia in adults. *Cochrane Database Syst Rev*. 2014;27(4):CD007938.
7. Mikkelsen S, Hilsted KL, Andersen PJ, et al. The effect of gabapentin on post-operative pain following tonsillectomy in adults. *Acta Anaesthesiol Scand*. 2006;50(7):809–815.
8. De Sarro G, Spagnolo C, Gareri P, Gallelli L, De Sarro A. Gabapentin potentiates the antiseizure activity of certain anticonvulsants in DBA/2 mice. *Eur J Pharmacol*. 1998;349(2–3):179–185.
9. Matsumura N, Nakaki T. Isobolographic analysis of the mechanisms of action of anticonvulsants from a combination effect. *Eur J Pharmacol*. 2014;741:237–246.
10. Hammond CJ, Niciu MJ, Drew S, Arias AJ. Anticonvulsants for the treatment of alcohol withdrawal syndrome and alcohol use disorders. *CNS Drugs*. 2015;29(4):293–311.
11. Caputo F, Bernardi M. Medications acting on the GABA system in the treatment of alcoholic patients. *Curr Pharm Des*. 2010;16(19):2118–2125.
12. Anton RF, Myrick H, Baros AM, et al. Efficacy of a combination of flumazenil and gabapentin in the treatment of alcohol dependence: relationship to alcohol withdrawal symptoms. *J Clin Psychopharmacol*. 2009;29(4):334–342.
13. Hepner S, Claxton R. Anti-epileptic drugs for pain #271. *J Palliat Med*. 2013;16(7):799–800.
14. Gidal BE, Radulovic LL, Kruger S, Rutecki P, Pitterle M, Bockbrader HN. Inter- and intra-subject variability in gabapentin absorption and absolute bioavailability. *Epilepsy Res*. 2000;40(2–3):123–127.
15. Johannessen Landmark C, Beiske G, Baftiu A, Burns ML, Johannessen SI. Experience from therapeutic drug monitoring and gender aspects of gabapentin and pregabalin in clinical practice. *Seizure*. 2015;28:88–91.
16. Scheschonka A, Beuche W. Treatment of post-herpetic pain in myasthenia gravis: exacerbation of weakness due to gabapentin. *Pain*. 2003;104(1–2):423–424.

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