Disturbance of consciousness and involuntary movements caused by pregabalin

Taro Shimizu,¹ Tsuneyasu Yoshida,² Koichi Kitamura,³ Osamu Hamada³

¹Department of General Medicine, Nerima Hikarigaoka Hospital, Tokyo, Japan
²Nippon Medical School, Tokyo, Japan
³Nerima Hikarigaoka Hospital, Tokyo, Japan

Correspondence to
 Dr Taro Shimizu,
 shimizutaro7@gmail.com

SUMMARY

A 91-year-old man with chronic low-back pain presented with 1-day history of disturbance of consciousness and myoclonus of all of his extremities and face. Laboratory examinations revealed no abnormalities. Administration of benzodiazepine for the myoclonus resulted in immediate and complete disappearance of the symptoms. He recently started taking pregabalin (Lyrica capsules) which was prescribed for low-back pain 3 days ago. The day following admission, he discontinued pregabalin. He did not experience recurrence of his symptoms any more. We concluded that the neurological symptoms he experienced were possibly due to pregabalin.

BACKGROUND

Differential diagnoses of disturbances of consciousness encompass a wide variety of aetiologies including familial, sporadic or secondary conditions such as drug-induced symptoms. As of July 2010, pregabalin (Lyrica capsule) has been approved in more than 110 countries and is recommended by principal medical societies including the International Association for the Study of Pain as first-line drug therapy for neuropathic pain. According to the product document sheet for Lyrica, 1084 of 1680 patients using pregabalin (64.5%) reported adverse effects. Major adverse effects include dizziness (22.5–23.4%), somnolence (15.9–24.5%) and oedema (10.75–17.2%), whereas serious side effects include angioedema (incidence unknown), renal failure (<0.1%), impaired consciousness (<0.3%), rhabdomyolysis (incidence unknown) and heart failure (<0.3%). Rare adverse effects include ataxia (>1%) and dyskinesia and myoclonus (0.3%).

In this case, we report drug-related disturbances of consciousness and involuntary movement that possibly were adverse effects of pregabalin.

CASE PRESENTATION

A 91-year-old man presented with disturbances of consciousness and involuntary movements. He had been suffering from chronic low-back pain, suspected of sciatic neuralgia. Three days prior to admission, he visited a local physician complaining of the pain. Based upon his persistent request of analgesics, only pregabalin of 150 mg/day was prescribed by the physician without conducting any detailed examinations. He took the medication following day. One day prior to admission, his grandson who was living with him noticed that he was somnolent, and had repetitive, involuntary twitching of his extremities and facial muscle. On arrival at the hospital, his symptoms still persisted. He was able to open his eyes spontaneously, although he

was unable to speak or comply with orders. On examination, no other abnormal findings were observed except for repetitive myoclonus of his upper and lower extremities and face. These involuntary movements could not be stopped by the patient despite instructions.

INVESTIGATIONS

Blood tests did not show any prominent findings. Urine toxicology study and blood culture were negative. Cerebrospinal fluid (CSF) analysis did not reveal any abnormal findings; no cells were present and CSF culture was negative.

Head CT and brain MRI showed no evidence of stroke or other intracranial lesions such as multiple sclerosis. Chest, abdominal and pelvic CT with enhancement did not show any suspicious lesions that may have caused the symptoms.

DIFFERENTIAL DIAGNOSIS

Differential diagnoses of loss of consciousness and involuntary movements are diverse and may have the following aetiologies: familial, sporadic or secondary conditions including multiple sclerosis, stroke, traumatic brain injury, infection, emotional imbalance or substances such as alcohol, caffeine and other medications. In our patient, CSF findings and brain MRI did not reveal any evidence of multiple sclerosis.

Furthermore, the patient's symptoms diminished following administration of benzodiazepine (BZ). After ruling out other aetiologies, an adverse effect of pregabalin was strongly suspected as the cause of his symptoms.

TREATMENT

Diazepam was administered (10 mg/2 ml) for the disturbances of consciousness and involuntary movements. Immediately after the infusion, the involuntary movements disappeared and his consciousness improved to the baseline. The day following admission, he discontinued pregabalin.

OUTCOME AND FOLLOW-UP

Although mild disturbance of consciousness and involuntary movements still persisted in the next day, they gradually diminished and finally disappeared by the continuous oral administration of diazepam (5 mg; three times a day) over the next 3 days. The day following of admission, he stopped to take pregabalin. He continued to take oral diazepam for 5 days resulted in complete resolution of the symptoms. Even after stopping to take diazepam, the symptoms did not recur. He was discharged 7 days after hospitalisation.

To cite: Shimizu T, Yoshida T, Kitamura K, et al. *BMJ Case Reports* Published online: 28 November 2012
 doi:10.1136/bcr-2012-007559

DISCUSSION

Pregabalin is an analgesic whose effect on peripheral and central neuropathic pain has been proven by many randomised double-blind studies.^{1–3} As of July 2010, it was used in more than 110 countries, and is now being considered in Europe and America as the first selective drug in medical treatment guidelines and algorithms for treating neuropathic pain including neuralgia following herpes zoster infections.^{4–9}

Pregabalin is a structural analogue of γ -aminobutyric acid (GABA), and although similar to gabapentin, is not metabolised to GABA and does not bind to GABA receptors (GABA_A, GABA_B) or many other receptors.¹⁰ In addition, pregabalin does not alter GABA uptake or degradation.^{11 12}

Pregabalin inhibits the influx of calcium ions by binding specifically to the $\alpha 2\delta$ subunit of voltage-gated calcium ion channels present in the presynapse of the excitability nervous system (end primary neurons).¹³ Inhibition of calcium ion influx causes a decrease in the release of neurotransmitters such as glutamate, leading to pain relief.^{14–17}

Severe side effects associated with pregabalin include heart failure (incidence <0.3%), rhabdomyolysis (incidence unknown), renal failure (incidence <0.1%) and angioedema (incidence unknown). It has been reported that the incidence of disturbances of consciousness and involuntary movements, such as in our case, is <0.3%. Loss of consciousness was reported in three cases in a clinical trial of post-herpetic neuralgia and in one case of diabetic peripheral neuropathy.

BZ enhance the action of GABA by binding to the BZ binding site ($\omega 1$) of the GABA_A receptor/BZ binding site/Cl-channel complex, thereby increasing the affinity of the receptor for GABA. A series of studies on the interaction of pregabalin and BZ indicate that pregabalin improves the dependence of BZ.^{18 19} Although further studies on this mechanism are necessary, BZ may compete with pregabalin, a GABA analogue, through an unknown mechanism.

In this case, disturbances of consciousness and involuntary movement which were thought to be one of the side effects of pregabalin disappeared following the administration of BZ. BZ may be effective for relieving central nervous system symptoms associated with pregabalin.

Competing interests None.

Patient consent Obtained.

REFERENCES

- 1 van Seventer R, Feister HA, Young JP Jr, *et al.* Efficacy and tolerability of twice-daily pregabalin for treating pain and related sleep interference in postherpetic neuralgia: a 13-week, randomized trial. *Curr Med Res Opin* 2006;22:375–84.
- 2 Sabatowski R, Gálvez R, Cherry DA, *et al.* 1008–045 Study Group. Pregabalin reduces pain and improves sleep and mood disturbances in patients with post-herpetic neuralgia: results of a randomised, placebo-controlled clinical trial. *Pain* 2004;109:26–35.
- 3 Dworkin RH, Corbin AE, Young JP Jr, *et al.* Pregabalin for the treatment of postherpetic neuralgia: a randomized, placebo-controlled trial. *Neurology* 2003;60:1274–83.
- 4 Dworkin RH, O'Connor AB, Backonja M, *et al.* Pharmacologic management of neuropathic pain: evidence-based recommendations. *Pain* 2007;132:237–51.
- 5 Finnerup NB, Otto M, McQuay HJ, *et al.* Algorithm for neuropathic pain treatment: an evidence based proposal. *Pain* 2005;118:289–305.
- 6 Attal N, Cruccu G, Haanpää M, *et al.* EFNS Task Force. EFNS guidelines on pharmacological treatment of neuropathic pain. *Eur J Neurol* 2006;13:1153–69.
- 7 Bril V, England J, Franklin GM, *et al.* American Academy of Neurology; American Association of Neuromuscular and Electrodiagnostic Medicine; American Academy of Physical Medicine and Rehabilitation. Evidence-based guideline: treatment of painful diabetic neuropathy: report of the American Academy of Neurology, the American Association of Neuromuscular and Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation. *Neurology* 2011;76:1758–65.
- 8 Moulin DE, Clark AJ, Gilron I, *et al.* Canadian Pain Society. Pharmacological management of chronic neuropathic pain—consensus statement and guidelines from the Canadian Pain Society. *Pain Res Manag* 2007 Spring;12:13–21.
- 9 Tan T, Barry P, Reken S, *et al.* Guideline Development Group. Pharmacological management of neuropathic pain in non-specialist settings: summary of NICE guidance. *BMJ* 2010;340:c1079.
- 10 Li Z, Taylor CP, Weber M, *et al.* Pregabalin is a potent and selective ligand for $\alpha(2)\delta-1$ and $\alpha(2)\delta-2$ calcium channel subunits. *Eur J Pharmacol* 2011;667:80–90.
- 11 Bialer M, Johannessen SI, Kupferberg HJ, *et al.* Progress report on new antiepileptic drugs a summary of the fourth Eilat conference (EILAT IV). *Epilepsy Res* 1999;34:1–41.
- 12 Lanneau C, Green A, Hirst WD, *et al.* Gabapentin is not a GABA_B receptor agonist. *Neuropharmacology* 2001;41:965–75.
- 13 Di Guilmi MN, Urbano FJ, Inchauspe CG, *et al.* Pregabalin modulation of neurotransmitter release is mediated by change in intrinsic activation/inactivation properties of $\text{Ca}(v)2.1$ calcium channels. *J Pharmacol Exp Ther* 2011;336:973–82.
- 14 Fink K, Dooley DJ, Meder WP, *et al.* Inhibition of neuronal $\text{Ca}(2+)$ influx by gabapentin and pregabalin in the human neocortex. *Neuropharmacology* 2002;42:229–36.
- 15 Errante LD, Petroff OA. Acute effects of gabapentin and pregabalin on rat forebrain cellular GABA, glutamate, and glutamine concentrations. *Seizure* 2003;12:300–6.
- 16 Cunningham MO, Woodhall GL, Thompson SE, *et al.* Dual effects of gabapentin and pregabalin on glutamate release at rat entorhinal synapses in vitro. *Eur J Neurosci* 2004;20:1566–76.
- 17 Micheva KD, Taylor CP, Smith SJ. Pregabalin reduces the release of synaptic vesicles from cultured hippocampal. *Neuron Mol Pharmacol* 2006;70:467–76.
- 18 Oulis P, Konstantakopoulos G, Kouzoupis AV, *et al.* Pregabalin in the discontinuation of long-term benzodiazepines' use. *Hum Psychopharmacol* 2008;23:337–40.
- 19 Bobes J, Rubio G, Terán A, *et al.* Pregabalin for the discontinuation of long-term benzodiazepines use: an assessment of its effectiveness in daily clinical practice. *Eur Psychiatry* 2012;27:301–7.

Learning points

- Pregabalin can cause involuntary movements.
- Benzodiazepine may be effective for relieving the involuntary movements and loss of consciousness caused by pregabalin.
- When there is no other cause which accounts for disturbances of consciousness, it is important to consider the possibility of a drug-related complication.

Copyright 2012 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit <http://group.bmj.com/group/rights-licensing/permissions>.
BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Become a Fellow of BMJ Case Reports today and you can:

- ▶ Submit as many cases as you like
- ▶ Enjoy fast sympathetic peer review and rapid publication of accepted articles
- ▶ Access all the published articles
- ▶ Re-use any of the published material for personal use and teaching without further permission

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

Visit casereports.bmj.com for more articles like this and to become a Fellow