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Pregabalin-induced parkinsonism: a case report with literature review

Zainab Mudher Mohammed[1], Shaymaa Fadhil Abbas[2]

[1]Pain Management Unit, Basrah Oncology Center, Basrah, Iraq
[2]Department of Pharmacology, Al-Zahraa College of Medicine, University of Basrah, Basrah, Iraq

ABSTRACT

Background. Pregabalin (PGB), an anti-epileptic medication approved for neuropathic pain and focal-onset seizures, has occasionally been linked to parkinsonism.

Case report. We report a suspected case of PGB-induced parkinsonism in a 65-year-old woman with post-herpetic neuralgia treated with PGB (75 mg/day). After receiving the third dose, she developed bradykinesia, movement difficulties, and postural tremor. Discontinuation of the drug led to complete resolution of symptoms within four days, supporting a drug-related effect.

Conclusion. Although rare, PGB-induced parkinsonism should be considered in patients presenting with new-onset movement disorders. Monitoring is particularly important in individuals with comorbidities.

Keywords: pregabalin, parkinsonism, drug-induced, movement disorders

INTRODUCTION

Parkinson's disease (PD) is a neurodegenerative disease characterized by relatively selective damage to dopamine neurons in the substantia nigra. It is characterized by motor features (bradykinesia, rigidity, tremor, gait disturbance, and postural instability) and nonmotor features such as psychiatric, cognitive, and autonomic manifestations. Meanwhile, parkinsonism represents a broad term describing any clinical condition characterized by motor symptoms similar to those observed in PD [1]. From an etiological perspective, approximately 80% of individuals with parkinsonism have degenerative causes. On the other hand, drug-induced parkinsonism (DIP) represents the most common form of non-degenerative parkinsonism. DIP occurs at an average yearly incidence rate of 3.3 per 100,000 person-years [2]. This condition is more common among older individuals, as age is the most evident risk factor for DIP [2,3], since dopamine concentrations decline and nigral cells degenerate with age. Another risk factor is female sex [2,3], suggesting that estrogen decreases the expression of dopamine receptors [4]. DIP is clinically characterized by bilateral and symmetrical symptoms, with more prominent rigidity and bradykinesia than in patients with PD [5].

DIP is commonly caused by dopamine-blocking medications or, in rare situations, other drugs such as calcium channel blockers, serotonin reuptake inhibitors (SSRIs), lithium, and antiepileptic drugs [6]. Pregabalin (PGB) is an antiepileptic medication often used to treat focal epileptic seizures, post-herpetic neuralgia, and neuropathic pain. It is suspected that PGB may reduce various neurotransmitters, resulting in diverse neurological manifestations as side effects, though the exact mechanism is not fully clear [7].

Since there have been few reports of PGB-induced parkinsonism, we present the current case, aiming to contribute to the pharmacovigilance literature by describing a rare, potentially reversible neurological adverse effect temporally associated with PGB use.

CASE REPORT

A 65-year-old woman presented to our pain management clinic with severe burning pain in the 7th and 8th dermatomes of the right chest (thoracic postherpetic neuralgia) of four months' duration. Her

Corresponding author:
Shaymaa Fadhil Abbas
E-mail: shaima.abbas@uobasrah.edu.iq

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past medical history for the last three years included ischemic heart disease and hypertension. Her drug history for these years included: aspirin 100 mg/day, rosuvastatin 20 mg/day, trimetazidine 35 mg/day, torsemide/spironolactone 10/50 mg, and candesartan 4 mg/day. The physician prescribed PGB 75 mg/day for the treatment of her post-herpetic neuralgia.

After three days, she developed dizziness, upper limb tremor, slowed movements, and inability to walk independently. The neurological examination revealed an alert, oriented patient with preserved speech and intact higher cortical functions. Cranial nerves examination was normal. The motor examination demonstrated symmetrical rigidity of the upper and lower limbs. The rigidity was uniform throughout the range of passive movement and was more pronounced in the upper limbs. Muscle bulk was preserved, with no observed fasciculations or involuntary movements. Muscle strength was preserved. A symmetrical postural tremor was present in the upper limbs. Deep tendon reflexes were normal, with bilateral flexor plantar responses. Sensory and coordination examinations were normal.

Gait assessment showed evident bradykinesia with reduced arm swing, and the patient was unable to walk independently, requiring assistance. She had no family history of movement disorders and had not recently taken any drugs that could cause parkinsonism. Given these findings, the physician suspected a probable link to PGB, and the drug was stopped immediately. The patient was referred for neurological consultation to exclude other causes. Structural neuroimaging studies and laboratory investigations were ordered, and they were unremarkable. The dopamine transporter scan was not performed due to its unavailability in our region. Four days later, the patient had nearly completely recovered. Formal UPDRS scoring was not applied due to rapid recovery. Written informed consent was obtained from the patient for publication.

DISCUSSION

The purpose of this study was to report an unusual case of probable DIP that developed shortly after low-dose PGB exposure. The diagnosis was solely clinical, and alternative etiologies were considered and excluded clinically. We were aware that the patient was on other medications, but we considered less likely the possibility that long-term use of those medications could cause DIP. According to a large body of published research, diuretics, angiotensin II receptor blockers (ARBs), statins, and antiplatelets are not commonly associated with DIP.

Regarding trimetazidine (TMZ), several studies have been conducted on TMZ use and related parkinsonism. In a systematic review that contained one retrospective study, one prospective study, two case reports, and one case series with no randomized clinical studies, there was a range of 4 months to 20 years between the beginning of symptoms and TMZ (dose, 60–80 mg/day) ingestion [8]. However, in our case, the symptoms started rapidly after PGB administration and resolved four days after it was stopped, while TMZ was continued. Given these characteristics, one could argue that PGB is associated with parkinsonism. Based on the close temporal relationship, symptom reversibility after drug withdrawal, and absence of alternative explanations, the association may be classified as probable according to established adverse drug reaction frameworks such as the WHO–UMC criteria.

PGB is approved as an adjuvant treatment for neuropathic pain related to diabetic peripheral neuropathy, post-herpetic neuralgia, fibromyalgia, and focal-onset seizures in patients aged 4 years or older. Off-label, this medication is also used to treat social anxiety disorder, bipolar disorder, generalized anxiety disorder, insomnia, and chronic pain [9]. It shares structural similarities with γ-aminobutyric acid (GABA), a substance that readily diffuses across the blood–brain barrier. Nevertheless, GABA receptors are not directly impacted by or bound by PGB. PGB primarily binds to the α2δ auxiliary subunit of presynaptic voltage-gated Ca^{2+} channels [9].

It has been found that acute administration of PGB decreases calcium currents [7,10], thereby reducing the release of several neurotransmitters such as serotonin, dopamine, noradrenaline, glutamate, and substance P [11,12]. The activity of PGB on these forms of channels, as well as their site, may explain the adverse consequences previously described in the studies. Central nervous system adverse effects are commonly reported in clinical practice. Mild to moderate severity adverse effects typically occur within the first two weeks after starting the drug and can result in about 15% of treatment discontinuations. In premarketing controlled trials, the most common adverse effects were weight gain, edema, dry mouth, impaired vision, dizziness, and somnolence [13].

PGB-related movement disorders (MDs) are infrequently reported. The most often reported MDs in multicentric studies were tremor and ataxia [14,15]. Due to a dearth of research, the specific pathophysiology underlying PGB-induced parkinsonism is unknown. Perez Lloret et al. suggested a hypothesis related to substance P [16]. Substance P is located in the basal ganglia and is currently investigated for its role in the pathogenesis of Parkinson's disease [17].

Substance P enhances inhibitory neurotransmission to the globus pallidus through its action on neu-

TABLE 1. Summary of case reports of pregabalin-induced parkinsonism

Reference	Patient's characteristics	Comorbidities	Drug history	Pregabalin dose, duration	Fate
Perez Lloret et al. [16]	A 64-year-old female	Type 2 diabetes mellitus	Not available	150 mg/day, three months	Recovery within 6 months
Masmoudi et al. [23]	A 58-year-old female	Hypertension, depression	Candesartan/ hydrochlorothiazide, clomipramine, propranolol	300 mg/day (duration not available)	Recovery following withdrawal
Prado-Mel et al. [24]	A 58-year-old female	Hypertension, anxiety, depression syndrome, acute on chronic renal failure (Contrast-induced)	Metformin, sitagliptin, enalapril, simvastatin, ezetimibe, fluoxetine	75 mg/day for three years Symptoms appeared 3 days following contrast imaging	Recovery within 10 days after drug withdrawal
Ari et al. [25]	A 53-year-old female	Hypertension	Irbesartan and thiazide	150 mg/day for 1 week	Recovery within 10 days of drug withdrawal
Ali et al. [26]	A 48-year-old female	Hypertension	losartan	300 mg/day for 5 days	Recovery within 7 days after withdrawal

rokinin-1 receptors and modulation of striatopallidal GABAergic pathways, thereby lowering thalamic inhibition and promoting movement [18]. In the presence of PGB, a reduction of these tachykinins is detected [19]. This can result in diminished inhibition of the globus pallidus, which increases thalamic inhibition and results in movement dysregulation [20]. However, all these mechanisms have been hypothesized but remain speculative in the absence of direct experimental confirmation.

To date, there are only a few case reports of PGB-induced parkinsonism (Table 1). We present a narrative review of these cases collected by searching the available literature on PubMed and Google Scholar. It is interesting to note that almost all case reports of PGB-induced parkinsonism were reported in female patients with a mean age of 57.6 years. Additionally, there were two case reports of PGB-associated muscle rigidity, which were interpreted by the authors as part of PD (not included in Table 1 due to limited data) [21]. Furthermore, a pharmacoepidemiologic study found that gabapentinoids (predominantly PGB) could be associated with parkinsonism [22].

CONCLUSION

This report highlights a probable association between PGB exposure and parkinsonism. While causality cannot be confirmed, clinicians should remain vigilant for new-onset movement disorders following PGB initiation. Larger pharmacovigilance studies and mechanistic investigations are needed to clarify this association.

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