

Prolonged encephalopathy and associated nonconvulsive seizures from suspected pregabalin and tapentadol: Two case reports and review of literature

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Abstract

A combination of pregabalin and tapentadol may be associated with prolonged encephalopathy.

KEYWORDS

antidepressants, nonconvulsive seizures, pregabalin, prolonged encephalopathy, tapentadol

1 | INTRODUCTION

Chronic pain may sometimes require treatment with combination of pregabalin and tapentadol. This combination may cause brief period of encephalopathy. However, prolonged encephalopathy associated nonconvulsive seizures (NCS) was not reported with these drugs. We report two cases of prolonged encephalopathy associated with a combination of tapentadol and pregabalin.

Neuropathic pain treatment with combination therapy is frequently used, despite lower level of evidence for such practice. Pregabalin (PGB), selective serotonin reuptake inhibitors (SSRI), serotonin noradrenaline reuptake inhibitors (SNRI), or tricyclic antidepressants (TCA) may be added as adjunct treatment when single agent therapy is unsuccessful or pain is associated with depression or anxiety.^{1,2} The use

of opioids for neuropathic pain is of limited benefit, with poor risk-benefit ratio,² but tapentadol have shown some positive results.^{2,3} The safety profile of the combination therapy of PGB and tapentadol has been studied is generally considered acceptable.^{4,5} However, fatigue, somnolence, behavioral changes, and even seizures have been reported in patients receiving PGB or tapentadol.⁶⁻⁹ The risk of serious side effects would even be more concerning when SSRI, SNRI, or TCA are further added to therapy. These side effects are brief usually reversible when the medications are withdrawn.⁹

In this article, we present two patients with prolonged encephalopathy associated with NCS admitted to our ICU with similar historical features, risks, and clinical findings. Consent was obtained from the patient or their legal next of kin for reporting these cases.

2 | CASE 1

A 51-year-old female patient presented to the emergency department (ED) with 24 hours of progressed altered conscious state and worsening agitation. She had suffered from chronic neuropathic pain affecting the lower limbs for which she had been on PGB and Tapentadol for a few years. Prior to admission, she was taking 300 mg of PGB twice a day with additional 75 mg capsules as required and 250 mg of tapentadol twice a day. Her other past medical history included depression managed with Paroxetine 20 mg daily, type-2 insulin requiring diabetes mellitus, and chronic obstructive pulmonary disease. She was an active smoker. She did not drink alcohol or use illicit substances, and she was unemployed. According to the family, the patient had been somnolent for 6 months spending most of every day sleeping and had had minimal social interaction. A week prior to presentation, the patient had just returned from a 10-day trip to Bali where she spent most of her time in the resort sleeping.

On presentation to the emergency department, the patient's Glasgow Coma Score (GCS) was 12/15 (eye 3, motor 6, and verbal 4) and was disorientated with one-word responses to questions. Her neurological examination was otherwise unremarkable including no rigidity, normal reflexes, and no clonus. Her respiratory and hemodynamic state were stable. In the context of worsening GCS, the patient was successfully intubated and subsequently admitted to ICU. She required propofol, midazolam, and fentanyl to keep her settled. Her initial provisional diagnosis was meningoencephalitis in the setting of altered conscious state, recent travel, and elevated white cell count of 21.1 cells (10^9)/L with a predominant neutrophilia of 18.1 cells(10^9)/L, although was not febrile. Her brain computed tomography (CT) and brain magnetic resonant imaging were reported normal. Her cerebrospinal fluid (CSF) examination revealed significantly elevated protein of 1.08 mg/dL and elevated glucose of 11.3 mg/dL and no cells found. She was commenced on Ceftriaxone, Benzyl Penicillin, and Aciclovir but were ceased when CSF gram stain, cultures, and viral PCR were reported negative. There was no microbiological growth identified in her blood cultures, respiratory secretions, and urine. Her serum urea or ammonia was not elevated (7.7 mmol/L and 36 μ mol/L). As the diagnosis was unclear, the patient was investigated with CT of chest and abdomen showing bilateral basal consolidation with no abnormality in abdomen and pelvis.

Despite weaning the sedation, the patient remained encephalopathic and concern of NCS was raised. On day 5, her EEG showed features of severe encephalopathy and epileptiform activity with no evidence of status epilepticus. The patient was loaded with Levetiracetam of 25 mg/Kg followed by a maintenance dose of 1000 mg twice daily, and later on Phenytoin of 20 mg/Kg loading with a maintenance dose of 300 mg/Kg was added due to persistent encephalopathy. The

neurological examination otherwise remained unremarkable. On day 15, a repeat EEG showed persistent severe encephalopathy, however, no epileptiform activity, whereas a repeat brain MRI was normal on day 18. A repeat CFS examination revealed glucose of 7.9 mmol/L and protein of 1.5 g/L. Other CSF related tests including viral specific antigen for Japanese encephalitis and 14-3-3 protein in CSF for Cruetzfeldt-Jacob were also negative. Limbic encephalitis was excluded when CSF voltage-gated potassium channel antibody, NMDA antibody, antivoltage-gated K^+ channel neuronal antibody, and CSF oligoclonal bands were negative. During the admission, the patient underwent more microbiological investigations which were negative. While waiting for the result of the CSF investigations for limbic encephalitis, she was commenced on methylprednisolone pulse therapy for three doses on three consecutive days based on advice from the neurology team. However, steroid therapy was discontinued when all subsequent autoimmune testing was negative.

Throughout the course of admission, the patient remained hemodynamically stable though intermittently requiring inotropes in the context of sedation. Percutaneous tracheostomy was performed for airway protection on day 12, as the patient remained encephalopathic. The encephalopathy gradually resolved to the extent where her tracheostomy was removed on day 35. The patient continued to neurologically improve and become more interactive. On day 37, she was discharged from ICU. In the ward, she made full neurological recovery and was discharged home on day 49. The prolonged epileptiform activity and encephalopathy were presumed to be due to PGB, and tapentadol given the lack of other attributable causes on extensive investigations.

3 | CASE 2

A 54-year-old female patient presented to ED with 2-day history of worsening confusion and intermittently altered conscious state. Her medical background included morbid obesity, hypertension, migraine, depression, anxiety, and chronic back pain due to osteoarthritis. Her chronic pain medications which she had been on for at least a year included PGB 75 mg twice a day tapentadol sustained release 200 mg twice a day and 50 mg twice a day as indicated. Her other medications were Aspirin 100 mg daily, Propranolol 40 mg daily, Duloxetine 30 mg daily, Amitriptyline 50 mg daily, Frusemide 20 mg daily, Amiloride /HCT 5/12.5 mg daily, and Elitriptan 80 mg daily when needed for migraines.

There was no history of smoking, alcohol abuse, or other substance addiction. She worked full time as phlebotomist. Her partner reported increasing somnolence and fatigue over approximately 6 months prior to admission. Few days before presentation, the patient became progressively confused. On presentation, her GCS was 13/15 with

no apparent seizure activity. The patient had stable respiratory and hemodynamic state and was not clinically septic. The brain CT did not reveal any abnormality. Her blood sugar, full blood examination, renal function, electrolytes, liver function test, and thyroid function test were within the normal range.

Due to a reduced conscious state and increasing agitation, she was admitted to ICU for monitoring and consequently was intubated and sedated. The cause for the reduced conscious state was unclear. Despite absence of fever and low yield for meningoencephalitis, ceftriaxone 2 g twice a day, Benzyl penicillin 2.4 g six times a day, and acyclovir 10 mg/Kg three times a day were commenced. CSF examination revealed elevated protein count of 1.6 mg/dL; however, the rest of her biochemistry and microbiology were within the normal range. CSF culture and viral PCR were negative. The patient remained severely encephalopathic despite interrupted sedation. An EEG performed on the day 4 of her admission indicated severe encephalopathy with no epileptiform activity. A repeat EEG on the following day showed features of severe encephalopathy and epileptiform discharges. Based on the EEG findings, the patient was commenced on Levetiracetam 1000 mg twice a day.

Due to unexplained cause for patient's condition, CT of the brain, chest abdomen, and pelvis was performed which revealed bilateral basal pulmonary consolidation with no significant abnormality otherwise. The investigations on blood for vasculitis were negative. Similar to case 1, limbic encephalitis was suspected; therefore, voltage-gated potassium channel antibody, NMDA antibody, and CSF oligoclonal bands were requested. While awaiting for the results, she was empirically pulsed with 1000 mg a day of methylprednisolone for a total of 3 days. Limbic encephalitis was excluded, and unsurprisingly, there was minimal effect to Methyl Prednisolone. On day 6, the patient became more awake and less agitated. On day 7, she was successfully extubated and 3 days later was discharged from ICU. Her repeat EEG in the neurology ward was normal. She spent two more days in the ward and was discharged to home with no neurological sequelae on day 12.

4 | DISCUSSION

In this report, we described two cases of prolonged severe encephalopathy associated with NCS, which we believe is secondary to a combination of PGB and tapentadol induced neurotoxicity. There are several causes of NCS in intensive care patients including hypoxic/anoxic brain injury, stroke, epilepsy, subarachnoid hemorrhage, traumatic brain injury, central nervous system infections, neoplasms of brain, sepsis, severe electrolyte abnormalities, metabolic disturbance associated with hyperglycemia, and drugs. In our cases, the

patients' historical information, clinical, laboratory, and imaging findings excluded neurological or systemic underlying problems.

Neurotoxicity of PGB and tapentadol has been well documented in previously published data, but they are generally short-lasting.^{8,10-12} However, to our knowledge, an unusually prolonged encephalopathy associated with NCS in the setting of a combination therapy of PGB and tapentadol has not been previously reported.

Pregabalin is a new generation gabapentinoid agent of anticonvulsant and analgesic property.¹³⁻¹⁵ It has been increasingly prescribed for neuropathic pain and postoperatively to reduce opioid use and reduce the risk of chronic pain. Its mechanism of action consists of modulation of $\alpha_2\delta$ subunit of voltage-gated calcium channels in CNS. Further, PGB reduces the release of several neurotransmitters, including glutamate, noradrenaline, and substance P. PGB is mostly cleared by kidneys; therefore, patients with renal impairment do require dosage reduction due to increased risk of accumulation, hence toxicity.¹⁶ Although considered relatively safe, serious neuropsychiatric adverse reactions associated with PGB such as delirium, encephalopathy, behavioral changes, or myoclonic status epilepticus have been reported.¹⁰ PGB-induced delirium, in older patients with multiple medical comorbidity and concurrent medications, is well reported; however, it may occur in young patients too.⁹ PGB-induced seizures respond well to stopping the drug and supportive measures.¹⁷ However, prolonged encephalopathy up to 48 hours post-PGB-induced seizures has been reported.⁸

Tapentadol is a synthetic mu-receptor agonist with 2-3 times lower affinity compared to morphine, but with additional noradrenaline (norepinephrine) reuptake inhibition within the CNS. The analgesic effect of tapentadol for management of neuropathic pain is attributed to its noradrenaline reuptake inhibition, which also accounts for its side effect profile.^{11,12} Similar to PGB, tapentadol is known to cause memory impairment, sedation, and coma.^{11,12} Convulsions associated with tapentadol use are thought to be due to mu-receptor agonist activity within the hippocampus leading to reduced gamma-aminobutyric acid (GABA) release rather than the typical serotonin reuptake inhibition mechanism that is associated with other analgesics and antidepressants.¹¹

In the recent years, concomitant administration of tapentadol and PGB has been practiced for their multimodal action in refractory neuropathic pain and often such patients are also on SSRI or SNRI like our two patients. Individually or combined, such therapy can be associated with significant morbidity from drug induced neurotoxicity in the form of neuropsychiatric features, altered mental state, and seizures¹⁸. In our two cases, there were no laboratory tests to confirm drug induced NCS and encephalopathy. However, drug induced neurotoxicity was strongly suspected when other differential diagnoses were exclusively ruled out.

The neurotoxicity may pass unrecognized when level of suspicion is not heightened. Unlike convulsive form, NCS is nonspecific. EEG may reveal periodic epileptiform patterns of indeterminate significance, similar to our patients' EEG findings. Further, the duration or frequency of NCS is unclear. Therefore, NCS requires high level of suspicion and if undetected it may contribute to a bad outcome. It is estimated that up to 37% of patients presenting with altered mental state suffer from NCS.¹⁹ The prognosis in NCS and related encephalopathy is overall determined by the underlying etiology and the time of resolution. Typically, recovery occurs once the underlying etiology is resolved or the drug responsible is withdrawn. Nevertheless, postictal encephalopathy may be prolonged despite therapy up to 10 days has been reported.²⁰ In a case series of 11 patients, postictal encephalopathy lasted between 4 to 10 days. Their EEG showed atypical encephalopathic pattern. Of 11 patients, nine had minimal CNS structural abnormalities. Although in our case report we could not prove causation, extensive investigations excluded a wide range of differential diagnoses. Therefore, drug-related prolonged encephalopathy was the most likely underlying etiology. With increasing incidence of combined PGB and tapentadol management particularly in chronic pain syndrome, caution has to be taken into account. Our patients' length of stay in ICU was significantly long exceeding 5 weeks in case 1 and 10 days in case 2. Case 1 also received tracheostomy which alone is not risk free. In addition, there was a substantial cost associated with the critical care provided.

5 | CONCLUSION

Combined PGB and tapentadol may be associated with significant and prolonged neurotoxicity. Morbidity from such treatment may result in prolonged ICU length of stay and increased healthcare cost. Adverse effects of combination of PGB and Tapentadol should be considered when somnolence is noted, and these drugs should be withdrawn.

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CONFLICT OF INTEREST

None of the authors have commercial association or financial involvement that might pose a conflict of interest in connection with this article.

AUTHOR CONTRIBUTION

Kavi Haji: involved in concept, data collection, drafting of manuscript, and revising for important intellectual content. Sachin Muthu and Iouri Banakh: involved in data collection, drafting of manuscript, and revising for important intellectual

content. Ravindranath Tiruvoipati: involved in drafting of manuscript and revising for important intellectual content.

ETHICS STATEMENT


Consent was obtained from the patient or their legal next of kin for reporting these cases.

DATA AVAILABILITY STATEMENT

All data that were available are reported in the manuscript.

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