NL Neurology Letters

Neurology Letters, 2025, 48– 52

doi: 10.61186/nl.4.1.48
Published Article
Case Report

CASE REPORT

Gabapentin and Baclofen Polypharmacy Presenting as Non-specific Abdominal Pain and Hyper-Reflexivity: A Case Report

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Abstract

Introduction: Gabapentin is a relatively safe medication and is frequently prescribed in large doses - upwards of 3600 mg per day. This along with baclofen are frequently prescribed together in patients suffering from neuropathy and muscle spasms. Despite these medications being widely known to be non-toxic, various case reports have outlined significant side effects secondarily to the use of these higher doses of medication. This in combination with other drugs (polypharmacy) can cause a toxidrome with both enteric and neurologic complications which is often overlooked.
Case Presentation: Herein, the authorial team discusses a 69-year-old patient who presented to an acute on chronic worsening of his long-standing non-specific abdominal symptoms of generalized pain and discomfort which lessened but did not resolve with defecation. During the history taking, careful questioning revealed that the patient had an increase in gabapentin dosage to the highest clinically indicated dosage of 3600 mg per day roughly one month prior in tandem with the use of 30 mg per day of baclofen. Along with the patient's chief complaint and history, a crucial physical exam with various neurological abnormalities, imaging, and lab findings helped cue the team into recognizing these symptoms as signs of a polypharmacy reaction. The patient's dosage of both medications were tapered which led to demonstrable clinical improvement of both the abdominal symptoms and the neurological symptoms.
Conclusions: This case report demonstrates the importance of a careful and complete history and physical examination when working with patients presenting to the emergency room with non-specific abdominal symptoms. The authorial team wants to highlight the importance of a broad differential to ensure that patients receive appropriate care. Lastly, only through the carefully crafted and thorough physical examination and history were the team able to narrow the differential and eventually find the correct diagnosis.

Key words: Gabapentin; Baclofen; Polypharmacy; History; Physical Exam

Introduction

Gabapentin has been known by many to be a relatively safe medication and, as a result, is frequently prescribed in large doses - upwards of 3600 mg per day based on the United States Federal Drug Administration Guidelines [1]. Despite gabapentin being widely known to be non-toxic, various case reports have outlined signif-

Recieved: 14 December 2024 Revised: 25 January 2024 Accepted: 30 February 2024 Published: 16 March 2025
The Journal For Neurologists, Neuroscientists, and Neurosurgeons.

Table 1. Pertinent Home medications for the patient's presentation

Name	Dosage	Frequency	Reason
Amlodipine	10 mg	Once Daily	Hypertension
Famotidine	20 mg	Once Daily	Heartburn
Baclofen	10 mg	Three Times a Day	Muscular Spasms
Gabapentin	600 mg	Three Times a Day	Neuropathic Pain
Polyethylene Glycol	17 gm	Once Daily	Constipation
Psyllium	1 teaspoon	Once Daily	Constipation
Simethicone	80 mg tab	Once Daily	Bloating

icant side effects secondarily to the use of these higher doses of medication. This has been shown to include severe myopathy, myoclonus, neutropenia, hypoglycemia, and altered mental status. In addition to the side effects mentioned, when additional agents that decrease neuronal activity are added (polypharmacy), there is a risk that the patient may develop other symptoms. Due to the assumed safety of these agents, the recognition of this as iatrogenic clinical etiology for the symptoms of a patient is often overlooked. Furthermore, there is a lack of attention brought to the effects of polypharmacy with gabapentin and other agents that decrease the tonicity of neuronal firing (Antispasmodics or Antiseizure medications) through published reports. In this case report we have a patient who presented to the emergency department due to gassy abdominal pain that was significant enough to affect his activities of daily life.

Case Presentation

The patient is a 69-year-old Male with a past medical history significant for hypertension, hyperlipidemia, peripheral neuropathy and an ependymoma at base of the neck s/p resection who had presented to the Emergency Department with a bloating feeling in the epigastric and hypochondriac regions of the abdomen for the past year with worsening severity starting three days prior to presentation. He rated it a 7/10 in severity, reported that it prevents him from carrying out his activities of daily living, and described the pain as constant and non-radiating. The patient denied having any abdominal surgeries. Pertinent home medications are included in Table 1.

Pertinent Medications

Objective Findings

On admission to the Emergency Department, the patient was afebrile, tachycardic at 109 beats per minutes, and normotensive. Upon completing a thorough physical examination, the patient was found to have mild tenderness of the abdomen diffusely to palpation with hyperactive bowel sounds. He had a negative Murphy's sign, no McBurney's point tenderness, no rebound tenderness, and did not demonstrate abdominal guarding. Upon completing a neurological function exam, he was found to be diffusely hyper-reflexive, 3+ bilateral upper and lower extremities, and had a positive jaw jerk reflex. He also had a wide based gait and was taking shuffling steps. In addition, he had left sided slowed rapid alternating hand movements and left sided mild pronator drift. His cremasteric reflex was absent but anal wink was present. Additional pertinent findings are found in Figure **??**.

Differential Diagnosis

Based on the patient's history and physical examination, several key diagnoses had to be considered. With the significant history of constipation and gas, and the need for laxatives and gas reducing

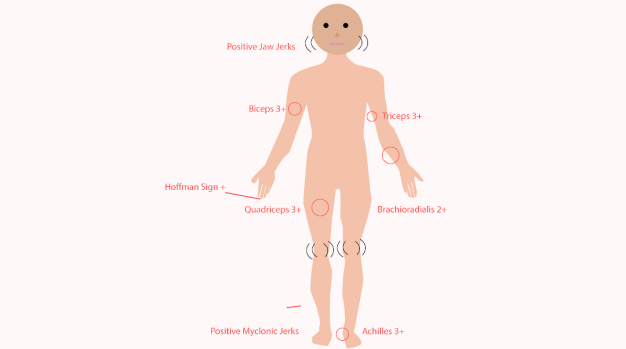

Figure 1. Key findings from the Neurological Examination

medications, along with the patient's reported sensation of feeling distended and gassy there was a concern for a bowel obstruction. This concern was magnified due to the acute change from the chronic constipation the patient normally had and how much the pain was affecting him. Nevertheless, without the classical distention of the abdomen and with the continued ability for the patient to pass flatus and feces this was deemed less likely.

There is also the history of an ependymoma at the base of the spinal cord that was resected. This is concerning for a potential spinal cord injury, whether it has developed secondary to the resection or if there is potentially a new mass causing neurogenic bowel problems. However, none of these explained the abnormal neurological symptoms which the patient presented with, therefore, this again led to spinal cord imaging being considered to be a less likely cause of the patient's presentation.

Lastly, based on the more chronic presentation with acute worsening, there was a concern that this might instead be a toxidrome, in which the patient was suffering from iatrogenic polypharmacy, food allergy or intolerances, or hypo-/hypervitaminosis. With this in mind, the team planned on obtaining abdominal imaging and lab values in order to get a better understanding of the patient. Further information regarding the differential diagnosis process is included in Table 2.

Laboratory Testing

On Admission

Imaging

Patient received a Computerized Tomography (CT) of the abdomen without contrast to assess for any bowel obstruction. The CT Abdomen showed that there were no signs of acute pathology but there was increased bowel gas seen with no obstruction, along with prostatomegaly and a nonobstructive stone in the left renal collecting system.

Diagnosis, Treatment and Hospital Course

After completion of the major work up, the team found that the patient was taking the highest dose of gabapentin for neuropathy and in addition was taking baclofen for muscle spasms. The CT image demonstrated increased gas amounts in the bowels with no obstruction. Based on the history and the physical examination, along with laboratories indicative of non-specific low levels of inflammation (CRP 43.9 mg/dL), it was determined that the next clinical steps would be to decrease the likely causes of the abdominal pain by decreasing the total daily dose of gabapentin and baclofen. The theory at that time was that the abdominal discomfort and bloating were secondary to likely decreased gut motility due to the high dose of gabapentin and co-administration of baclofen. This theory also explained hyperreflexia and tremulousness on exam secondary to a negative myoclonus which has been reported secondary to these agents, especially when co-administered or in high doses.

To test this theory for the patient's abdominal discomfort and his co-existing tremulousness and hyperreflexia on exam, the gabapentin dose was tapered down to a total reduction of the dose by 30%, ultimately being gabapentin 400 mg three times a day. His baclofen was also tapered down by a total of 20%, making the dose of baclofen 5 mg twice a day.

Over the patient's hospital stay overnight, the patient's abdominal symptoms had slowly improved. The pain was likely due to a large amount of gas in the bowels and as such the patient was given a bowel regimen consisting of propyl ethylene glycol and senna twice a day. He did experience increased neuropathic pain, as expected with the reduction in gabapentin, however this did resolve by itself over the patient's stay.

Discussion

Throughout the initial work up of this patient, a careful history was key in leading the practitioners to the potential causes of the patient's non-specific abdominal symptoms. In the recent literature, the best practice in the work up of a patient with non-specific abdominal pain is a thorough history and physical examination modified with potential Point of Care Ultrasonography [2, 3]. The rationale being that patients can provide specific details of their pain profiles which can lead a physician to add to the differential or remove from the differential. In the use of this tool, the patient can be saved from the use of additional radiation through Computerized Tomography testing.

Importance of a Thorough Physical Exam

In the case of this patient, while he was suffering from a simple sounding bowel problem it was key that the team fulfill their duty and perform a full medical history, medication reconciliation, and full physical examination. Only in performing this was the true diagnosis of gabapentin toxicity able to be discerned allowing us to taper off of his medications. Gabapentin side effects are frequently overlooked, with many patients suffering from the side effects of the drug at normally therapeutic (800-3200 mg/day) dosages [4]. These side effects as seen in the retrospective chart review published in *Epilepsia* in the early 2000s demonstrated that 13 out of 104 patients suffered the side effect of myoclonus, which lead the authors to conclude that they are fairly common and clinically irrelevant. In these patients, all of them were on multiple antiepileptic drugs and the side effect was only reported in those patients on multiple agents [5].

Since that initial publication several case reports were published which demonstrated other major side effects of gabapentin in which patients experienced a toxidrome from the medication. In a case report published in *Clinical Neuropharmacology*, a patient on low dose gabapentin (900 mg/day) developed bilateral asterixis as a side effect of the gabapentin, which ceased after the medication was discontinued [6]. Similarly, in a publication in *Progress in neuro-psychopharmacology & biological psychiatry*, two patients were presented one on low dose gabapentin (900 mg/day) and standard dose oxcarbazepine who developed asterixis and another on high dose gabapentin (3600 mg/day) who developed encephalopathy – in both cases these symptoms subsided with the discontinuation of the gabapentin [7]. In patients with decreased renal function, there was a report of experiencing encephalopathy with on a single 300 mg dose of the drug [8]. Lastly, in patients on supratherapeutic doses (>3600 mg/day) there have been reports of patients suffering from side effects such as a myokymia [9].

Theorized Polypharmacy Mechanism of Action

The theoretical mechanism of action for gabapentin is decreased synaptic transmission secondary to decreasing activity of voltage gated calcium preventing the release of neurotransmitters and thus decreasing the activity of ligand gated sodium channels on the post synaptic neuron (Figure 3) [10, 11, 12, 13]. Gabapentin has a specific affinity for the alpha 2 delta subunit on voltage gated calcium channels and no other known high-affinity binding locations have been found as of the writing of this article (Figure 3) [10, 11, 12, 13]. While there was some initial theories that there might be direct binding effects on the GABA receptor, these were later found to inaccurate theories on the mechanism of action [10, 11, 12, 13]. In 2019, some data showed that there is a role that gabapentin plays

Table 2. Differential diagnosis reasoning table

Differential Diagnosis	Reasons it was considered	Reasons it was less likely
Bowel Obstruction	Acute on chronic symptoms and severe pain	No classical abdominal distention. Pain did not follow the classical colic pattern of pain seen in this condition.
Spinal Cord Injury	Diffuse hyperreflexia and myoclonic jerking (Potentially clonus)	Timeframe from the surgical removal of the ependymoma. Lack of frank weakness and lack of frank sensation loss. Presence of the Jaw jerk reflex where the innervation is above the level of the spinal cord.
Toxidrome	Diffuse hyperreflexia and myoclonic jerking	Patient denied any exposure to toxins including illicit drugs.
Food Allergy or Intolerance	Bloating feeling in the epigastric and hypochondriac regions	Patient denied any specific foods or food types making this worse.
Iatrogenic Cause	Patient on multiple medications that slow the movement of food through the GI tract	None - This was deemed to be the most likely cause.

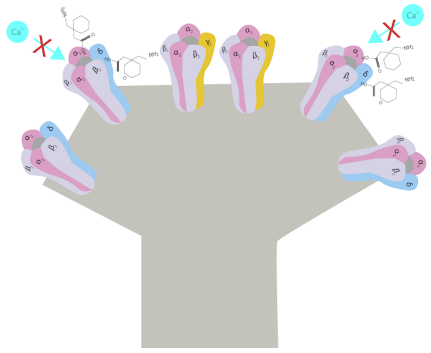

Figure 2. The currently accepted mechanism of action for Gabapentin on the neuron

on increasing the expression of the δ-subunit-containing GABA-A receptors [14]. In recent papers, gabapentin has been implicated in decreasing the overall tonicity of the enteric nervous system [15]. This is thought to be from the drug actually causing an increase of GABA release from glial cells and secondarily through promoting the synthesis of GABA through increasing the activity of the GABA producing enzyme L-glutamate decarboxylase in the human enteric nervous system [15]. Therefore, this plus the effects from baclofen, a GABA-B activator, likely lead to the abdominal discomfort and bloating sensation [16]. In some reported case studies, baclofen alone has been demonstrated to cause what is known as a pseudo-obstruction in which the patient will suffer from all the major effects of a bowel obstruction but without any evidence of actual blockage, just due to the adynamic effect of the baclofen on the gut [17]. Therefore, based on the patient's presentation, he likely was suffering from a toxidrome of decreased tonicity within the gut from both the gabapentin's effect on the gut and the baclofen's effect on the gut [15, 16, 17]. This toxidrome would be from the synergistic suppression of neuronal activity from the two drugs that can act on the enteric nervous system. Thus, it is recommended based off this case and others like it that polypharmacy be taken

Table 3. Laboratory results

Test	Result	Reference/Comment
Lactic Acid	1.19	
Hemolysis	No Hemolysis	
Lipemia	No Lipemia	
Icterus	No Icterus	
Lipase	10	
AST	18	
ALT	12	
BUN	18	
Glucose	160	
Sodium	138	
Potassium	3.7	
Chloride	103	
tCO_2	24	
Calcium	9.7	
Protein	6.8	
Albumin	4.0	
Bilirubin, total	0.8	
Alkaline Phosphatase	102	
Anion Gap	11	
Creatinine	1.07	
C-Reactive Protein	43.9	
eGFR	75	
INR	1	
PT	13	
WBC	6.1	
MPV	11.6	
RBC	4.72	
Hgb	14.7	
HCT	43.2	
MCV	91.5	
MCH	31.1	
MCHC	34.0	
RBC Distribution Width CV	14.6	
Absolute Neutrophils	3.28	
Absolute Lymphocytes	2.17	
Absolute Monocytes	0.50	
Absolute Eosinophils	0.06	
Absolute Basophils	0.06	
Absolute Immature Granulocytes	<0.03	
PLT	287	
Influenza A (DNA)	Negative	
Influenza B (DNA)	Negative	
COVID-19 (Cepheid)	Not Detected	
RSV (Cepheid)	Negative	

into consideration, especially when anatomical causes have been ruled out.

Figure 3. The currently accepted mechanism of action for Gabapentin on the neuron

Conclusion

This case report highlights the importance of medication list reconciliation and evaluation of the medical necessity of each of the pharmacological agents. It was only through reduction of the medication that we were able to attribute the symptoms the patient experienced to the increase in gabapentin dosage in combination with the co-administration of baclofen. This case also highlighted the importance of a thorough physical examination, including a full neurological assessment. In our exam we were able to connect neurological findings, hyperreflexia and positive jaw jerk reflex, to the abdominal findings ultimately pointing us towards the patient's presentation being due to a toxidrome from his polypharmacy.

Conflict of Interest

The authors declare that there are no significant conflicts of interest.

Funding

None was utilized in the writing of this case report.

Author Contributions

V.S., L.S., T.C.V, and A.S. all were involved in the writing of the initial case report and providing significant edits in order to ensure the scientific accuracy of the article. M.S. created and revised the clinical images for the article and worked with the team in order to provide clear images for use in the article based on the most current research. V.S., L.S., M.S., T.C.V, and A.S. all provided grammar edits and were a part of finalizing the draft for submission.

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