A Possible Case of Gabapentin-Induced Mild Hyperglycemia

Journal of Pharmacy Technology
2014, Vol. 30(4) 140–144
© The Author(s) 2014
Reprints and permissions:
sagepub.com/journalsPermissions.nav
DOI: 10.1177/8755122514524925
pharmatech.sagepub.com

Jennifer Andres, PharmD, BCPS¹, Jennifer N. Clements,
PharmD, BCPS, CDE, BCACP², and Donna Salmiery, PharmD³

Abstract

Objective: A possible case of gabapentin-induced mild hyperglycemia is reported. **Case Summary:** A 63-year-old Caucasian gentleman was treated in a pharmacist-run pharmacotherapy clinic for type 2 diabetes management. His comorbidities included type 2 diabetes mellitus, hypertension, dyslipidemia, coronary artery disease, peripheral vascular disease, Barrett's esophagus, chronic back pain, and obesity. His medications for these comorbidities were continued throughout his care. The patient had no known drug allergies. After 3 months of pharmacist-managed diabetes management, the patient's glucose levels had improved and were within the desired range for a majority of the readings. The patient was consulted to the pain clinic for uncontrolled pain and initiated and titrated on gabapentin from 300 mg per day to 600 to 900 mg 3 times per day. Two weeks later, the patient's glucose levels increased to levels of 150 to 165 mg/dL. The patient's increasing blood glucose values were treated with NPH insulin, which was titrated for several months until he was switched to insulin glargine. Gabapentin was not discontinued since it provided adequate pain control. **Discussion:** An objective causality assessment revealed that the adverse effect was possible. No other new medications were introduced, current medications were not adjusted, and no alternate causes could be found for increased glucose values. **Conclusion:** A 63-year-old Caucasian gentleman with type 2 diabetes mellitus developed a possible case of gabapentin-induced mild hyperglycemia after receiving gabapentin for several months with a dose titration. Gabapentin could be considered as a cause for otherwise unexplained hyperglycemia in a patient.

Keywords

gabapentin, drugs, adverse reactions, hyperglycemia, glycemic control

Introduction

Gabapentin was approved by the Food and Drug Administration in 1994 and is indicated for the treatment of postherpetic neuralgia and epilepsy.¹ Although it is structurally similar to γ -amino butyric acid (GABA), its exact mechanism of action is unknown as it prevents allodynia and hyperalgesia.¹ Proposed mechanisms of gabapentin have been documented in the literature.² Gabapentin does cross the blood–brain barrier and is renally eliminated, which requires dose adjustments.^{1,3} In comparison to placebo, the most common adverse events with gabapentin (as defined by >10% frequency of occurrence in package insert) included dizziness, somnolence, and peripheral edema.¹ While these adverse events may be mild to moderate in intensity, the medication may be intolerable for a patient leading to discontinuation.¹ According to the package insert, metabolic adverse events may occur with gabapentin, when compared to placebo. Approximately 1.2% of patients treated with gabapentin may experience hyperglycemia when compared to 0.4% with placebo.¹ Hypoglycemia has also been reported as an infrequent adverse event in the package insert.¹ A search of the medical literature revealed one case report of

gabapentin-induced hypoglycemia in a long-term peritoneal dialysis patient without a history of diabetes and a randomized trial that found no difference in glycemic control between placebo and gabapentin-treated groups.^{4,5} Therefore, this case report is the first published possible adverse reaction of gabapentin-induced hyperglycemia with a review of the literature.

Case Report

The patient is a 63-year-old gentleman with type 2 diabetes mellitus who was consulted to a pharmacist-run pharmacotherapy clinic. The patient stands 72 inches tall and weighed

¹Philadelphia College of Osteopathic Medicine School of Pharmacy, Georgia Campus, Suwanee, GA, USA

²Presbyterian College School of Pharmacy, Clinton, SC, USA

³Martinsburg Veterans Affairs Medical Center, Martinsburg, WV, USA

Corresponding Author:

Jennifer Andres, PharmD, BCPS, Philadelphia College of Osteopathic Medicine School of Pharmacy, Georgia Campus, 625 Old Peachtree Road NW, Suwanee, GA 30024, USA.

Email: jenniferan@pcom.edu

Table 1. Hemoglobin (Hgb) A_{1c} Values Over Time.

Date	Hgb A _{1c}
T = 0 weeks (presentation to clinic)	7.5%
T = 18 weeks	7.1%
T = 30 weeks	7.4%
T = 60 weeks	7.8%

Table 2. Other Pertinent Laboratory Data During Period of Increasing Blood Glucose Values.

Laboratory Data	34 Weeks	60 Weeks
SCr	1.0	1.1
WBC	10.33	—
Total cholesterol	134	125
Triglycerides	248	285
HDL	42	39
LDL	42	28.9

Abbreviations: SCr, serum creatinine; WBC, white blood cell; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

268 pounds (122 kg) on presentation to the pharmacotherapy clinic on his initial visit. Family history was unremarkable—there was no history of diabetes, stroke, or myocardial infarction. The patient is married and his wife attends all clinic appointments with him. The patient is a retired mechanic. He denied alcohol or illicit drug use but smoked approximately half a pack of cigarettes per day. He denied any allergies to any medications, but stated that atorvastatin gave him joint pain. Medication lists, including prescription products and over-the-counter products, were verified at each visit. Compliance was also assessed at each visit. The patient stated compliance with all medications. Blood glucose values checked twice daily as directed by the clinic also helped confirm the patient's adherence to therapy. Additionally, the patient attended all of the scheduled clinic visits including telephone appointments. The patient used a One Touch glucometer for blood glucose monitoring at home. Pertinent laboratory values during the patient's care can be found in Tables 1 and 2. Please see Table 3 for a timeline of the patient's visits.

The patient was initiated on NPH insulin at the initial pharmacotherapy visit with continuation of oral medication (metformin 1000 mg twice daily and glipizide 20 mg twice daily). An intermediate-acting insulin (ie, NPH insulin) was titrated based on glucose readings during follow-up encounters approximately every 2 weeks. Approximately 34 weeks after the initial visit to the pharmacotherapy clinic, the patient's glucose averages were as follows: 7 days = 123, 14 days = 138, and 30 days = 138 mg/dL. These glucose averages correspond to preprandial readings (prebreakfast and predinner). He was injecting 21 units of NPH insulin at bedtime with prescribed doses of metformin and glipizide. He

reported no other medication changes besides initiation of gabapentin 300 mg (1 capsule) at bedtime; he initiated this medication and dose the night prior to the pharmacotherapy clinic appointment. He also mentioned a consultation to a pain specialist at the Medical Center. Therefore, he did not have any complaints regarding diabetes management. The majority of this visit focused on the patient's complaints of pain, which had been previously rated as 10/10. The patient's wife indicated that the pain was so extreme during the day and with movement that he was unable to participate in social events. No changes were made at the pharmacotherapy visit regarding the patient's diabetes regimen of NPH insulin, metformin, and glipizide as pain was uncontrolled. Controlling the patient's pain with gabapentin would decrease blood glucose values.

The patient was consulted and scheduled in the pain clinic during week 38 for uncontrolled right side pain. The patient had a history of right side pain for the previous 6 years. The pain started atraumatically with a cyst in this area. While the cyst was removed, the pain remained as a chronic issue without any effect from local injections, lidocaine patches, and oxycodone. At the time of the pain clinic appointment, the patient was taking amitriptyline 50 mg at bedtime, tramadol 50 mg 3 times per day along with gabapentin 300 mg at bedtime (no changes in the dose as previously documented at a pharmacotherapy visit) for pain control. It was difficult for the patient to describe the type of pain as sharp, shooting, or dull. The patient had an improvement from pain scale (9-10 to 5-6 out of 10) following initiation of gabapentin. During this visit, gabapentin was titrated from 300 mg per day to 300 mg 3 times per day due to neuropathic pain and some effective response with a lower dose. Alternative plans were provided within the progress note from the pain clinic, if gabapentin titration was ineffective for the pain. During week 40, the patient's gabapentin dose was titrated to 600 mg in the morning, 300 mg in the afternoon, and 600 mg in the evening.

Fourteen days after the initial pain visit (week 42), the patient was contacted by the pharmacist to review glucose readings. The 30-day average for glucose readings was 150 mg/dL with only 3 glucose values (out of 32) within the desired preprandial goal of 70 to 130 mg/dL. Based on this objective information, NPH insulin was changed from 21 to 24 units at bedtime. The patient was contacted again 2 weeks later and glucose readings were averaging 153 to 158 mg/dL for 7-, 14-, and 30-day averages. He did not provide specific glucose readings but the patient indicated frustration regarding worsening glucose readings. Another insulin titration was made from 24 to 27 units at bedtime. A face-to-face visit was scheduled to discuss future options for diabetes management. At week 46, the patient presented with average glucose readings of 158 to 165 mg/dL and a couple of values spiking above 200 mg/dL, which had not occurred at previous visits. In addition, none of the glucose readings were within the desired preprandial range

Table 3. Timeline of Events.

Visit	Timeframe	Pertinent Medications	Blood Glucose Values (If Applicable and Recorded at Visit)
1	0 weeks (patient consulted to the pharmacotherapy clinic)	NPH insulin initiated 5 units QHS Metformin continued 1000 mg BID Glipizide continued 20 mg before breakfast and dinner	
2	2-14 weeks	NPH insulin titrated up to 21 units QHS Metformin and glipizide continued	
3	26 weeks	NPH insulin, metformin, and glipizide continued at current doses	
	34 weeks (encounter 1)	Gabapentin initiated at dose of 300 mg QHS	
4	34 weeks (encounter 2)	NPH insulin, metformin and glipizide continued	Average readings 123-138 for 7, 14, and 30 days 138 mg/dL 14-day average (n = 38) 138 mg/dL 30-day average (n = 60)
	38 weeks (initial pain clinic appointment)	Gabapentin titrated to 300 mg TID	
5	40 weeks	NPH insulin increased to 24 units Metformin and glipizide continued Gabapentin titrated to 600 mg in AM, 300 mg in PM, and 600 mg QHS	Average readings 150 mg/dL for 30 days
6	42 weeks	NPH insulin increased to 27 units	Average readings 153-158 mg/dL for 7, 14, and 30 days
		Metformin and glipizide continued	
7	46 weeks	NPH discontinued Glargine 30 units at bedtime initiated Metformin and glipizide continued Gabapentin titrated to 600 mg TID	Average readings of 158-165 mg/dL 7, 14, and 30 days 158 mg/dL 7-day average (n = 13) 159 mg/dL 14-day average (n = 27) 165 mg/dL 30-day average (n = 60)
8	49 weeks	Glargine dose increased to 34 units Metformin and glipizide continued	Average readings of 147-160 for 7, 14, and 30 days

of 70 to 130 mg/dL. During this visit, the patient mentioned gabapentin was effective for his pain at a dose of 600 mg 3 times per day (1800 mg per day). The patient was switched to insulin glargine (LANTUS) 30 units at bedtime and oral medications (metformin and glipizide) were continued in order to control blood glucose. At the next visit after starting insulin glargine, glucose averages had improved, with the 7-, 14-, and 30-day averages of 147, 151, and 160 mg/dL, respectively. Insulin glargine was further titrated up to 34 units at bedtime when patient was called for follow-up. Gabapentin was continued due to pain control. Gabapentin was assumed effective for pain relief due to a decrease in pain score (1/10 from 10/10) and complaints of pain were not made at visits following initiation of gabapentin therapy.

Discussion

No similar case report has been documented in the literature to date. Additionally, the clinical trial that allowed

gabapentin to come to market documents a small risk of hyperglycemia.

This case report scored a 4 on the Naranjo et al scale of causality, classifying the case report as “possible” of gabapentin-induced hyperglycemia.⁶ There are multiple etiologies of hyperglycemia for a patient with diabetes. We first considered uncontrolled pain as a cause diagnosis for a mild elevation in glucose levels. Raz and colleagues proposed adequate pain thresholds among patients with diabetes despite more secretion of opioid peptides endogenously from the antagonistic properties of glucose.⁷ Therefore, a patient with diabetes neuropathy would have compromised pain mechanism through excessive nociceptive impulses or failed secretory response from endogenous opioid receptors.⁷ Second, we considered other etiologies of hyperglycemia related to pain management, such as insomnia or excessive food intake. During the pharmacotherapy visits, the patient and wife denied these etiologies. There was no documentation of insomnia or excessive caloric or carbohydrate intake within

the pain clinic progress notes. Glycemic control can worsen over time and could be a potential confounder to this case report. However, gabapentin dose was titrated up as described in the case report with subsequent up-titrations in insulin dose, all while glucose values increased, despite decreasing levels of pain, which leads to gabapentin being considered a contributing factor. The patient's weight increased slightly from his entrance to the pharmacotherapy clinic at 268 pounds to 272 pounds at gabapentin initiation; however, no documentation was provided that these weights were taken on the same scale or the same time of day. Additionally, this weight increase represents a just over 1% increase from baseline. The patient had no other changes to medications apart from diabetic regimen and initiation of gabapentin.

The patient's A₁C was noted to increase from week 18 to week 30, prior to initiation of gabapentin therapy. Prior to the A₁C being drawn during week 30, the patient complained of increased pain during a clinic appointment. The patient stated that he thought the pain could be affecting his blood glucose values. Despite adequate pain control achievement following gabapentin initiation, blood glucose values continued to rise.

From a search of the medical literature, 2 articles speak to the effect of gabapentin on blood glucose levels. Backonja and colleagues⁵ conducted a randomized, double-blind, placebo-controlled, parallel arm, multicenter study to determine the efficacy and safety of gabapentin as monotherapy for diabetes neuropathy. The study assessed 165 patients with uncontrolled type 1 or type 2 diabetes mellitus (hemoglobin A₁C levels of 11% or less). Seventy-five percent of patient had a diagnosis of type 2 diabetes mellitus. During the intent-to-treat study, there was a 7-day screening phase and 8-week double-blind phase. Patients were randomized to either gabapentin or placebo during the double-blind phase. Titration of gabapentin occurred during the first 4-week period of this phase; the dose increased weekly from 900 mg per day (week 1) to 3600 mg per day (week 3). A fixed dose of gabapentin was continued, as tolerated, during the second 4-week period of the double-blind phase. Approximately 68% of patients achieved the maximum dose of gabapentin at 3600 mg per day. There were no changes in hemoglobin A₁C levels; however, the authors did not report baseline or treatment levels most likely due to short duration of the study.⁵ Therefore, it is difficult to conclude any possible change in glycemic control during this study.

In the second article, a case report of hypoglycemia was described in a 58-year-old female with end-stage renal disease on peritoneal dialysis with no history of diabetes mellitus.⁴ The patient had been taking a stable dose of gabapentin for 2 years (300 mg per day). The dose was increased to 300 mg twice daily 1 month prior to a hospital admission for hypoglycemia, hypotension, dizziness, and fatigue. The patient was treated with symptomatic and supportive therapy.

Gabapentin was discontinued and hypoglycemia resolved 3 days later with 10% dextrose drip.⁴

Therefore, based on the case report and reported hyperglycemia in clinical trials, it seems gabapentin can cause mild blood glucose disturbances for an unknown mechanism of action. It is difficult to determine the true incidence or causality of gabapentin-induced hyperglycemia due to the lack of documentation in the medical literature. There are several reasons for the lack of knowledge for this possible adverse event. The number of possible reports may not reflect actual number of cases. If gabapentin causes any fluctuations in glucose levels, modification of drug therapy is warranted to correct the abnormalities and an association with gabapentin may go unnoticed. In addition, the number of patients with diabetes receiving gabapentin may not be known at a specific point in time. There are many reasons for fluctuating blood glucose control, which may make it difficult to determine the causality of a single factor. Last, there is no established casual relationship for gabapentin and glucose fluctuations and the mechanism of such as interaction is unknown. Clinicians should consider gabapentin as a contributing factor to glucose fluctuations in the absence of other causes. Insulin therapy should be adjusted based on these values.

Conclusion

A 63-year-old Caucasian gentleman with type 2 diabetes mellitus developed a possible case of gabapentin-induced mild hyperglycemia after receiving gabapentin for several months with a dose titration. Gabapentin could be considered as a cause for otherwise unexplained hyperglycemia in a patient.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: The Department of Veterans Affairs supported this publication. "This material is the result of work supported with resources and the use of facilities at the Martinsburg, West Virginia VA Medical Center."

References

1. Neurontin [gabapentin]. New York, NY: Pfizer; 2011.
2. Taylor CP, Gee NS, Su TZ, et al. A summary of mechanistic hypotheses of gabapentin pharmacology. *Epilepsy Res.* 1998;29:233-249.
3. Ojemann LM, Friel PN, Ojemann GA. Gabapentin concentration in human brain. *Epilepsia.* 1988;29:694.

4. Penumalee S, Kissner PZ, Migdal SD. Gabapentin-induced hypoglycemia in a long-term peritoneal dialysis patient. *Am J Kidney Dis.* 2003;42(6):E3-E5.
5. 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;280:1831-1836.
6. Naranjo CA, Busto U, Sellers EM, et al. A method of estimating the probability of adverse drug reactions. *Clin Pharmacol Ther.* 1981;30:239-245.
7. Raz I, Hasdal D, Seltzer Z, Melmed RN. Effect of hyperglycemia on pain perception and on efficacy of morphine anal in rats. *Diabetes.* 1988;37:1253-1259.