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Gabapentin-induced bilateral lower extremity edema in a patient with pervasive developmental disorder and schizoaffective disorder

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Abstract

Gabapentin binds to the alpha-2-delta subunit of presynaptic voltage-gated calcium channels and is used for a wide variety of on- and off-label indications. Gabapentin is dosed at total daily doses ranging from 300 to 3600 mg/d, which is generally divided into 3 doses. Although gabapentin is generally well tolerated, 1 potential reported adverse effect is peripheral edema. However, due to the extensive number of etiologies of peripheral edema, medication causes may be overlooked on an inpatient psychiatric unit. This is a case of delayed identification of a probable adverse drug reaction to gabapentin (Naranjo score of 5) consisting of painful, 4+ pitting bilateral edema and a clear dose relationship in a patient with pervasive developmental disorder and schizoaffective disorder.

Keywords: gabapentin, peripheral edema

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Background

Gabapentin binds to the alpha-2-delta subunit of presynaptic voltage-gated calcium channels and is used for a wide variety of indications both Food and Drug Administration approved and off-label.[1-3] It is approved by the Food and Drug Administration to treat postherpetic neuralgia and epilepsy[4] with common off-label indications including fibromyalgia, anxiety, mood disorders, and sleep disorders.[2] Gabapentin is dosed at total daily doses ranging from 300 to 3600 mg/d, which is generally divided into 3 doses due to the dose-dependent saturation of its absorption in the small intestine.[1,4] Although gabapentin is generally well tolerated, 1 reported potential adverse effect is peripheral edema.[4-11] However, due to the extensive number of etiologies of peripheral edema, medication causes may be overlooked on an inpatient psychiatric unit. This is a case of painful, 4+ pitting bilateral edema with a probable association to gabapentin (Naranjo score 5) and a clear dose relationship in a patient with pervasive developmental disorder and schizoaffective disorder utilizing gabapentin for mood stabilization.

Case

A 46-year-old, African American male with no known medication allergies and a past medical history of schizoaffective disorder, pervasive developmental disorder, poorly controlled type 2 diabetes, hypertension, hypothyroidism, and obesity was admitted to the psychiatric ward for increasing aggressive behaviors at a group home. He was initiated on gabapentin 400 mg 3 times daily (1200 mg/d) 7 months prior to admission by his outpatient psychiatrist for mood stabilization, an off-label

indication of gabapentin. He was reported to be adherent by group home staff, and they assisted the patient with medication administration. In addition to gabapentin, he was prescribed aspirin, atorvastatin, divalproex sodium extended-release, docusate, insulin glargine, insulin lispro, levothyroxine, lisinopril, loxapine, metformin, pyridoxine, sitagliptin, and trazodone. The patient's sodium on admission was 136 mmol/L, and the rest of his electrolytes were also within normal limits. Additionally, his thyroid panel was within normal limits, and his total valproic acid concentration was 90 mcg/mL. Gabapentin was initially held on admission in an attempt to change this medication to a mood stabilizer with more evidence for efficacy. However, the patient's guardian would not consent to other mood stabilizers and wanted to optimize his outpatient regimen. Therefore, gabapentin was restarted on hospital day 7. On hospital day 10, the dose of gabapentin was increased to 600 mg 3 times daily (1800 mg/d) for additional mood stabilization. On hospital day 20, the patient developed mild edema halfway up his shin that was bilateral and nonpitting and for which a medicine consult was obtained. Three days later, on hospital day 23, the patient was reported by the medicine consult team to have pedal edema greater in the right side than the left, and the patient reported pain in his feet. However, he denied symptoms of dyspnea, orthopnea, or other symptoms consistent with a cardiovascular etiology. The patient had hyponatremia with a serum sodium of 132 mmol/L when the medicine team evaluated him, but the rest of his electrolytes were within normal limits. Later that same day, the on-call resident was paged for bilateral edema and blood glucose >400 mg/dL. The patient was sent to the emergency department to be evaluated where he was noted to have 4+ pitting edema and pain in bilateral lower extremities. After all common medical etiologies were ruled out, including heart failure, diabetic ketoacidosis, and venous thrombosis, the patient was discharged back to the behavioral health unit with a recommendation to wear compression socks and decrease fluid intake as it was thought that the patient's hyponatremia was hypervolemic and contributing to his edema. For the next 7 days, the patient continued to experience bilateral, painful, 3 to 4+ pitting edema despite compression socks and fluid restriction. On hospital day 31, after 21 days at 1800 mg/d, gabapentin was identified by the resident pharmacist as a potential cause of the patient's edema, and the dose was decreased to 300 mg 3 times daily (900 mg/d). Other medications in the patient's regimen with the potential to cause peripheral edema were divalproex sodium,[12] loxapine,[13] and trazodone.[14] However, there were no other medication changes to his outpatient regimen, and the peripheral edema started during the current hospitalization. The next day, after the gabapentin dose was decreased, the treating psychiatrist noted an improvement in the patient's edema. Gabapentin was discontinued 2 days later, and the edema resolved within 1 week. Serum sodium increased to 135 mmol/L when the patient allowed labs to be obtained 11 days after gabapentin discontinuation. The patient had no recurrence of edema for the last month of admission after gabapentin discontinuation.

Discussion

On an inpatient psychiatric unit, medications are often overlooked as a possible cause of new peripheral edema or other potential medication-related adverse events. This case illustrates the importance of a pharmacist perspective within the interdisciplinary team as the pharmacist was the person who proposed gabapentin as a potential cause of edema after 3 weeks of symptoms. Although medical causes should be ruled out, it is also important to look for medication causes, especially considering the most recent changes to a patient's medication regimen. In this case, it could have avoided unnecessary interventions, such as compression socks and fluid restriction, when a medication could easily be adjusted or discontinued. This patient had both gabapentin[4] and divalproex sodium[12] that had the greatest potential to have caused peripheral edema. However, he had been tolerating divalproex sodium for a couple of years, and the peripheral edema was new since the start of this hospitalization and gabapentin titration.[12] A review of gabapentin using the Naranjo algorithm[16] indicates a score of 5 (probable) because there are previous conclusive reports of this potential adverse effect (+1), edema appeared after gabapentin administration (+2), it was more severe when the dose was increased (+1), it improved after gabapentin discontinuation (+1), and it was confirmed by objective evidence (+1). However, there were alternate causes for the edema (-1), but these were ruled out as described in the case. The other medications prescribed to this patient with reports of edema are trazodone[13] and loxapine,[14] but his outpatient doses were not adjusted since the development of edema. Because his other medications were ruled out and gabapentin had a Naranjo algorithm score of 5, it was tapered off and was found to be a probable cause.

Peripheral edema induced by gabapentin has been reported to have an incidence of 2% to 8%.[4,8,9] It is generally considered to be dose related and more common in the geriatric patient population as reported by a pooled analysis of adverse effects from 3 clinical trials of gabapentin utilized for postherpetic neuralgia.[10] The incidence of peripheral edema in this analysis increased from 1.4% to 7.5% at doses ≥1800 mg/d. The highest reported incidence of peripheral edema was 12.3% at 3600 mg/d. The case presented supports the hypothesis that this adverse effect is likely dose related because the patient was maintained on gabapentin 1200 mg/d with no

reported edema for 7 months prior to hospitalization. It was only after the dose was increased to 1800 mg/d that the patient developed this potential side effect.

Peripheral edema from gabapentin is not always dose related, however. There are 3 published case reports[6,7,11] of patients who developed peripheral edema at doses lower than 1800 mg/d. One case published by Kanbay et al[6] described peripheral edema related to gabapentin in a 76-year-old male. The authors reported bilateral pretibial edema after 3 weeks of gabapentin 300 mg/d for neuropathic pain. Within 3 days of discontinuation of gabapentin, the edema resolved. When the patient was rechallenged with gabapentin, the edema returned after 5 days, suggesting the authors' suspicions of an adverse effect from gabapentin was likely correct. The gabapentin was then permanently discontinued with resolution and no recurrence of edema. Additionally, Kahlon et al[7] reported a case of a 46-year-old male with schizoaffective disorder who was prescribed 300 mg twice daily for his anxiety. He developed worsening 3+ lower extremity edema causing discomfort during ambulation. His electrolytes, including serum sodium, were all within normal limits. Gabapentin was discontinued, and his edema improved over the next few days. The final case, reported by Bidaki et al,[11] described a 48-year-old male with depression and insomnia who experienced severe localized edema that resolved upon discontinuation of gabapentin 300 mg at bedtime.

Although the mechanism behind peripheral edema from gabapentin is largely unknown, it has been theorized to be similar to the mechanism in which other calcium channel blockers (eg, amlodipine) cause peripheral edema.[6,7] This relationship has been hypothesized to be due to gabapentin's actions on presynaptic voltage-gated calcium channels.[1,6,7] Calcium channel blockers cause peripheral edema due to peripheral arteriolar dilation without compensation in the venous system.[13] The incidence of peripheral edema from calcium channel blockers has also been shown to be dose related and more common in the elderly, comparable to the reports of gabapentin-induced edema.[15] Likely by a similar mechanism, pregabalin is another medication to consider as a cause for peripheral edema.[1]

In the case described above, peripheral edema secondary to hyponatremia was first thought to be the potential cause prior to gabapentin identification by the resident pharmacist. This patient was younger than most previously reported case reports as this adverse effect has been reported to be more common in the geriatric patient population. Additionally, other case reports describe edema that develops early in treatment with gabapentin, and this patient was maintained on gabapentin 1200 mg/d for 7 months prior to admission without evidence of peripheral edema. This patient case represents an important occurrence of gabapentin-induced peripheral edema that was initially overlooked as medication-related on the inpatient psychiatric unit.

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