Original Article

Hyponatremia Associated with Pregabalin

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ABSTRACT

Objective: To assess if hyponatremia is associated with pregabalin. Pregabalin, an analog of the neurotransmitter γ-aminobutyric acid, possesses analgesic, anticonvulsant, and anxiolytic properties.
Study Design: A prospective randomized interventional trial study
Place and Duration of Study: This study was conducted at the Jinnah Hospital dialysis center from 01st January 2021 to 31st December 2021.
Materials and Methods: All the patients with hyponatremia & taking pregabalin were included in the study. Although hyponatremia (when serum sodium level below 135 mmol/L) is the most common abnormality of electrolytes observed in hospitalized patients, it is typically associated with certain drugs such as diuretics, antidepressants, and antiepileptic medications. Notably, hyponatremia as a side effect of pregabalin has not been reported due to its relatively recent introduction. However, we present a few clinical scenarios where it is highly probable that hyponatremia was associated with pregabalin.
Results: Out of 60 patients with hyponatremia, ten were found to be taking pregabalin. Three out of 10 (30%) cases of hyponatremia were found to be associated with pregabalin. These case scenarios are discussed in detail in the main body of this study.
Conclusion: While hyponatremia is an infrequent occurrence, it is a potential side effect of pregabalin. Therefore, caution should be exercised when prescribing pregabalin to patients who are at a higher risk of developing hyponatremia
Key Words: Pregabalin, hyponatremia, electrolyte disorders.

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INTRODUCTION

Pregabalin, an analog of the neurotransmitter γ-aminobutyric acid, exhibits analgesic, anticonvulsant, and anxiolytic properties. It is primarily used as an anticonvulsant for various conditions such as pain of diabetic neuropathy, neuralgia after herpes, fibromyalgia, seizure disorder, and nerve pain associated with spinal cord injury. In clinical trials, Pregabalin was generally tolerated well, and most side effects because of pregabalin were dose dependent. These adverse effects were typically mild or moderate in intensity and resolved on their own.

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The most common adverse effects of Pregabalin were related to the central nervous system, including dizziness (reported in 8-43% of cases), somnolence (6-30%), weight gain (5-20%), ataxia (2-21%), lower extremity edema (3-19%), amblyopia (1-17%), disturbed thinking (1-10%), and double vision (2-13%). Other adverse effects observed in clinical trials included asthenia, euphoria, dryness of mouth, headache, constipation, nausea, confusion, tremor and vertigo. Among the adverse effects reported, dizziness and somnolence were the most frequent reasons for discontinuation of treatment.
Although hyponatremia has rarely been reported in association with Pregabalin use (2-3 case reports), it is worth noting that it is not a commonly recognized side effect. In this case series, we present three patients who developed hyponatremia, which is most likely attributed to the use of pregabalin.

MATERIALS AND METHODS

All the patients with hyponatremia & taking pregabalin were included in the study from 1/1/2021 till December 31, 2021. Although hyponatremia (when serum sodium level below 135 mmol/L) is the most common abnormality of electrolytes observed in hospitalized patients, it is typically associated with certain drugs such as diuretics, antidepressants, and antiepileptic

medications. Notably, hyponatremia as a side effect of pregabalin has not been reported due to its relatively recent introduction. However, we present a few clinical scenarios where it is highly probable that hyponatremia was associated with pregabalin.

RESULTS

Scenario No. 1: A 65-year-old female patient with a significant past medical history of hypertension, HCV positivity, hypothyroidism, and depression presented to the emergency room (ER) with symptoms of shortness of breath, nausea, generalized weakness, and poor oral intake that had been ongoing for four days. Prior to hospitalization, she had been in her usual state of health but started feeling sick, initially experiencing a dry cough and nausea followed by a loss of appetite. The next day, she developed dyspnea, prompting her family to bring her to the ER.

Upon arrival at the ER, her vitals were: blood pressure of 120/70 mmHg, pulse rate of 80 beats per minute, oxygen saturation of 98%, and a temperature of 99.8°F. She was admitted to the hospital for possible respiratory tract infection or viral pneumonia. Her past surgical history included cholecystectomy, total abdominal hysterectomy, and spinal surgery. She had no known drug allergies and denied alcohol, smoking, drug use, as well as the intake of over-the-counter or herbal medications. Her current medications included omeprazole, amlodipine, losartan, bisoprolol, thyroxine, pregabalin, and acetaminophen.

During the examination, her blood pressure was measured at 130/80 mmHg, pulse rate at 76 beats per minute, with no fever. Oxygen saturation was 97%, respiratory rate ranged from 18 to 20 breaths per minute, and her Glasgow Coma Scale (GCS) score was 15/15. She appeared alert, awake, and oriented in terms of time, place, and person, and did not show signs of acute distress. However, she displayed mild lethargy, sluggish responses, and occasional confusion, although she answered most questions appropriately. No pallor, jaundice, or cyanosis was observed. Her pupils were equal in size, round, and reactive to light and accommodation, and her extraocular movements were intact bilaterally. Her neck was supple with no thyroid swelling, lymphadenopathy, or jugular venous distention. Upon chest examination, decreased breath sounds were detected bilaterally at the bases, along with decreased air entry. Cardiac examination revealed normal audibility of the first and second heart sounds, without any gallop, rub, or murmur. The abdomen was soft, non-tender, and non-distended, with no ab normal bowel sounds or organomegaly. The extremities showed no signs of cyanosis, clubbing, or edema.

Laboratory data indicated the following: The CBC showed a TLC of 4.6k, hemoglobin level of 11.8 g/dL, platelet count of 180k, and a polymorphonuclear (PMN) percentage of 75%. The blood urea nitrogen (BUN) level was 12 mg/dL, creatinine level was 0.6 mg/dL, serum sodium level was 103 meq/L, chloride level was 74 meq/L, potassium level was 2.9 meq/L, bicarbonate level was 21 meq/L, magnesium level was 1.3 meq/L, erythrocyte sedimentation rate (ESR) was 18, and B-type natriuretic peptide (BNP) level was 324. Serum osmolality was measured at 220 mosm, random urinary sodium was 30 meq/L, and urinary osmolality was 130 mosm/L. Thyroid-stimulating hormone (TSH) and thyroid function tests were normal, as was the cortisol level and uric acid level. Liver function tests were normal. The electrocardiogram (ECG) showed first-degree atrioventricular (AV) block, and the chest X-ray revealed decompensated heart failure and cardiomegaly. A kidney sonogram showed normal results, while the echocardiogram indicated an ejection fraction (EF) of 65%, grade 1 diastolic dysfunction, no wall motion abnormalities, and mild mitral regurgitation.

The patient was placed on water restriction, administered intravenous furosemide 40 mg twice a day, and pregabalin was discontinued. Her serum sodium levels gradually improved to 108, 121, 131, and 136 on days 1, 2, 3, and 4, respectively. Pregabalin was discontinued upon discharge. However, during a follow-up visit two weeks later, her serum sodium was found to be 125. Further review of her medications revealed that she had mistakenly started taking pregabalin again a few days prior. After discontinuing pregabalin, her serum sodium increased to 134 after three days. Given that she was exposed to pregabalin for the second time and developed hyponatremia that improved upon discontinuation, it was concluded that pregabalin was likely responsible for her hyponatremia.

Scenario No. 2: A 75-year-old woman with a significant past medical history (PMHx) of coronary artery disease status post coronary artery bypass grafting (CABG), hypertension, diabetes, osteoarthritis, dementia, and decubitus ulcers was diagnosed with post-herpetic neuralgia and started on pregabalin (Lyrica) two months ago. She was transferred from a nursing home to the hospital for evaluation of altered mental status, and upon examination, she was found to have a serum sodium level of 115. There were no apparent signs of volume depletion or hypervolemia during her clinical assessment. Her blood pressure was measured at 110/70 mmHg, heart rate at 90 beats per minute, and her chest, cardiac, abdomen, and extremity examinations were within normal limits. However, she did have a grade II decubitus ulcer on her back. Her current medication regimen included aspirin, clopidogrel, metoprolol, enalapril, furosemide, pregabalin, tramadol, acetaminophen, alprazolam, and a multivitamin.

Laboratory data revealed a potassium level of 4 meq/L, creatinine level of 1.2 mg/dL, blood urea nitrogen (BUN) level of 34 mg/dL, chloride level of 89 mg/dL,

sodium level of 115 meq/L, uric acid level of 6 mg/dL, hemoglobin level of 11 g/L, and a white blood cell count (WBC) of 12 with 80% polymorphonuclear cells (PMNs). Thyroid function tests and cortisol levels were normal. Serum osmolality was measured at 241 mosm/kg, urine sodium at 26 meq/L, and urine osmolality at 325 mosm/kg. Chest X-ray findings were normal, while urine analysis showed 5-10 white blood cells and positive leukocyte esterase. Urine culture confirmed the presence of Klebsiella pneumoniae, and treatment with levofloxacin was initiated.

To address the hyponatremia, the patient received two boluses of 100 cc of hypertonic saline, and pregabalin was discontinued. Gabapentin was initiated to manage the neuropathic pain associated with post-herpetic neuralgia. Her serum sodium level increased to 124 the following day and gradually rose to 138 over the next week without requiring additional intravenous fluids. As there were no other apparent causes for the hyponatremia, and considering her euvolemic status based on normal findings of urine specific gravity, serum hemoglobin, BUN, creatinine, and uric acid levels, it was determined that the hyponatremia was likely due to the use of pregabalin. Notably, her last recorded serum sodium level from two months prior to starting pregabalin was within the normal range at 140 mmol/L. After discontinuing pregabalin, her serum sodium level normalized, and her mental status returned to normal. Throughout the subsequent six months of follow-up, her sodium levels remained within the normal range. This case was managed in Texas, USA, under my care.

Scenario No. 3: A 65-year-old patient with a significant PMHx of diabetes mellitus for 30 years, high blood pressure for 20 years, and end-stage renal disease (ESRD) undergoing maintenance hemodialysis for 5 years was also diagnosed with diabetic neuropathy, retinopathy, CKD-related mineral bone disorder, anemia, and secondary hyperparathyroidism. Due to his condition, he had been following dietary restrictions on phosphorus, sodium, potassium, and water. His monthly routine laboratory tests consistently showed normal results, except for mild hyperkalemia, hyperphosphatemia, elevated parathyroid hormone (PTH) levels (>600 pg/mL), and anemia with hemoglobin levels ranging from 9 to 12 g/dL. However, during his latest monthly labs, his sodium level (usually ranging from 131 to 139 mmol/L) was recorded at 122 mmol/L. A thorough review of his medical records and medications was conducted, and a physical examination was performed. Aside from edema and decreased breath sounds at the lung bases, the rest of the examination did not reveal any notable findings. The patient's blood pressure was measured at 160/100 mmHg, heart rate at 65 beats per minute, and he had a well-functioning left radiocephalic arteriovenous fistula with a palpable bruit and thrill. Upon further questioning, he denied consuming an excessive amount of water. Further investigation revealed that his primary care physician had recently prescribed pregabalin and escitalopram during his last visit. Pregabalin was prescribed to manage worsening diabetic neuropathic pain after amitriptyline proved ineffective, while escitalopram was prescribed for clinical depression. Both medications were discontinued, and his serum sodium increased to 132 after 3 days. In an attempt to identify the likely cause, we cautiously reintroduced pregabalin, suspecting that escitalopram was responsible for the hyponatremia. Surprisingly, his sodium levels dropped to 129 three days after restarting pregabalin and then decreased further to 124 after a week. Pregabalin was promptly discontinued again, resulting in an improvement in serum sodium levels. Currently, the patient has been taking escitalopram for 4 weeks, and his serum sodium levels have remained within the normal range.

DISCUSSION

The application of the 'Naranjo algorithm' to these cases resulted in scores ranging from 6 to 8, confirming that hyponatremia was likely secondary to pregabalin (table 1). The exact mechanism of hyponatremia is uncertain, with possibilities including increased sodium loss in urine[1] or syndrome of inappropriate antidiuretic hormone secretion (SIADH) [3] as reported by others. While these explanations may account for hyponatremia in the first two cases, they do not fully explain the condition in the third case, as the patient had end-stage renal disease (ESRD) and was oliguric. Although excessive water intake in this oliguric patient cannot be ruled out, the improvement of hyponatremia upon discontinuation of pregabalin and its recurrence upon re-administration strongly suggest that pregabalin was the cause. Another possibility is the increased effect of antidiuretic hormone and subsequent retention of free water, leading to expansion of extracellular fluid. Additionally, pregabalin's known side effect of dry mouth may have contributed to increased water intake, despite patients seemingly denying excessive water consumption. Furthermore, except for the first case where urinary osmolality was 130 mosm/kg of water, urinary osmolality was found to be high in all other cases.

In Case No. 1, the cause of hyponatremia could be decompensated heart failure, which responded to intravenous furosemide and discontinuation of pregabalin. Although the patient had a history of hypertension and grade 1 diastolic dysfunction, there was no history of coronary artery disease or cardiomyopathy, and the ejection fraction was normal. Therefore, hyponatremia was presumed to be secondary to increased antidiuretic hormone or heart failure.

There have been recent case reports suggesting a potential association between pregabalin administration and exacerbation of chronic heart failure. Three cases were documented, where patients with clinically stable

heart failure experienced possible heart failure exacerbation after receiving pregabalin for neuropathic pain.[5] Furthermore, volume 4.1 of the SIDER database reports hyponatremia as an infrequent side effect of pregabalin.[4]

Table No.1: Naranjo Algorithm

Question	Yes	No	Do Not Know	Score
1. Are there previous conclusive reports on this reaction?	+1	0	0	
2. Did the adverse event appear after the suspected drug was administered?	+2	-1	0	
3. Did the adverse event improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0	
4. Did the adverse event reappear when the drug was readministered?	+2	-1	0	
5. Are there alternative causes that could on their own have caused the reaction?	-1	+2	0	
6. Did the reaction reappear when a placebo was given?	-1	+1	0	
7. Was the drug detected in blood or other fluids in concentrations known to be toxic?	+1	0	0	
8. Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0	
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0	
10. Was the adverse event confirmed by any objective evidence?	+1	0	0	
			Total	

(Naranjo CA et al. "A method for estimating the probability of adverse drug reactions". Clin Pharmacol. Ther. August 1981)

The Adverse Dug Reaction is assigned to a probability category from the total score as follows:
Definite: >8 Probable: 5 to 8 Possible: 1 to 4 Doubtful : <1

Another case report published in the Journal of Case Reports (JCR) described a 55-year-old male who presented with a serum sodium level of 108 meq/L after two weeks of starting pregabalin 75 mg once daily for neuropathic pain secondary to L4, L5 radiculopathy. Based on clinical and laboratory data, SIADH secondary to pregabalin was presumed, and sodium levels promptly normalized within 3 days of discontinuing pregabalin. The patient showed clinical and biochemical improvement after stopping the medication and had a serum sodium level of 132 mmol/L at the two-week follow-up.[3]

Ehealthme.com reported the following data regarding hyponatremia and the use of Lyrica (pregabalin) on their website: Among 138,585 individuals who reported side effects while taking Lyrica, 546 people (0.39%) experienced hyponatremia. The risk of hyponatremia was higher in females over the age of 60 who had been taking the drug for less than one month, also took Nexium, and had depression.[6]

CONCLUSION

While hyponatremia is an infrequent occurrence, it is a potential side effect of pregabalin. Therefore, caution should be exercised when prescribing pregabalin to patients who are at a higher risk of developing hyponatremia.

Author's Contribution:

Concept & Design of Study:	Shafiq urrehman Cheema
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Conflict of Interest: The study has no conflict of interest to declare by any author.

REFERENCES

1. Blommel ML, et al. Pregabalin: An Antiepileptic Agent Useful for Neuropathic Pain. Am J Health Syst Pharm 2007;64(14):1475-1482.
2. Blum A, Simsolo C, Tatour I. Hyponatremia and confusion caused by pregabalin. The Israel Med Association J : IMAJ 2009;11(11):699-700.
3. Sudhagar M, Aneesh B, Nayyar I. et al. Syndrome of Inappropriate Anti-diuretic Hormone Secretion and pregabalin-a critical alert on a potentially reversible side-effect. J Case Reports 2014,4(2): 408-411.
4. Kuhn M, Letunic I, Jensen LJ, Bork P. The SIDER database of drugs and side effects. Nucleic acids research 2016;44(D1): D1075-9.
5. Robert Lee Page II, Cantu M, Lindenfeld J, Hergott LJ, Lowes BD. Possible heart failure exacerbation associated with pregabalin: case discussion and literature review. J Cardiovascular Med 2008; 9(9):922-5.
6. Schmidt D. Drug treatment of epilepsy: options and limitations. Epilepsy Behavior 2009;15(1): 56-65.