Case Report

Pregabalin Induced Syndrome of Inappropriate Anti-Diuretic Hormone (SIADH) Secretion: A Case Report

Metwali H, Hasan H, Yousuf M

King Abdul Aziz Medical City, Western Region, Jeddah, Saudi Arabia

ABSTRACT

Pregabalin is now being frequently used to treat many medical conditions such as fibromyalgia, diabetic peripheral neuropathy, post herpetic neuralgia and as adjunctive therapy for seizure. Hyponatremia is the most frequent electrolyte abnormality seen in hospitalized patients. And, Syndrome of Inappropriate Anti-diuretic Hormone Secretion (SIADH) is a common cause of euvolemic hyponatremia. Despite Hyponatremia, SIADH and use of Pregabalin being common in clinical practice, there are only a few case reports of Pregabalin induced SIADH causing hyponatremia which are reported in our literature. The aim of this case report is to add to the existing reports about the incidence of hyponatremia due to pregabalin which will alert the prescriber to monitor serum sodium levels and identify the cause of hyponatremia in patients newly started on pregabalin.

Key words: Pregabalin; Syndrome of Inappropriate Anti-Diuretic Hormone (SIADH)

Correspondence:

Hend Metwali, Pharm, Clinical Pharmacist, Pharmaceutical Care Department at King Abdullah International Medical Research Center / King Saud bin Abdulaziz University for Health Sciences, King Abdulaziz Medical City –Jeddah

Saudi Arabia

E-mail: metwalihe@nhga.med.sa
metwalihe@nhga.med.sa

Access this article online

Website: www.jbclinpharm.org

Quick Response Code:

INTRODUCTION

Hyponatremia, defined as a serum sodium concentration below 135 mmol/L, is the most common electrolyte imbalance encountered in clinical practice, occurring in 15%-30% of acutely or chronically hospitalized patients. [1] It causes a diverse spectrum of clinical symptoms ranging from mild to life threatening, with higher overall mortality. [2,3]. Several populations are at increased risk of developing hyponatremia, including intensive care unit, postoperative, psychiatric, elderly, and nursing home patients. [4-8]

Euvolemic hyponatremia occurs when the water intake exceeds the excretion by kidney. SIADH is the most common cause of euvolemic hyponatremia. The criteria necessary for its diagnosis were originally defined by Bartter and Schwartz in 1967. [9] [Table 1]. Many causes have been implicated with SIADH like tumors, CNS disorders, pulmonary infections and medications.

Drugs known to mimic the action of Arginine Vasopressin [AVP], stimulate its release, or enhance its action can cause SIADH. [10-13] Selective Serotonin-Reuptake Inhibitors for example can also enhance the Arginine Vasopressin [AVP] effect, especially in the elderly, females, those taking diuretics, or those with low baseline plasma sodium concentrations. [10,12] Wide range of medications contribute to cause SIADH such as Phenothiazines, Tricyclic anti-depressant [TCA], Serotonin Reuptake Inhibitors, Opiate derivatives, Carbamazepine and Others. There are only a few reported cases about SIADH induced by Pregabalin. This is a case report of patient who developed hyponatremia secondary to SAIDH after being started on Pregabalin.

CASE REPORT

A 28-year-old male patient presented to emergency department on December 20th 2018 with an acute onset of abnormal movements characterized by up-rolling of both eyes, non-purposeful rapid unequal movements of both upper and lower limbs and clenching of teeth. His other symptoms were generalized fatigue and weakness associated with decreased oral intake over the last two days. He had been on Gabapentin for peripheral neuropathy which was stopped and he was switched to Pregabalin 75 mg twice daily a week before this presentation. He has a past medical history of autosomal recessive combined cerebellar and peripheral ataxia with hearing loss, diabetes mellitus, hypothyroidism, von Willebrand disease and intellectual disability.

His laboratory investigation showed serum sodium 115 mmol/L. He appeared mildly dehydrated and therefore the initial working diagnosis was hypovolemic hyponatremia. He received 1 liter of intravenous 0.9% Normal Saline, which improved his sodium level to 119 mmol/L. Following this he was kept on 0.9% Normal Saline at 30 ml/hour and his sodium reached to 121 mmol/L. As there was no significant improvement in his serum sodium levels and the patient remained lethargic, he was given 2% hypertonic saline, despite which his serum sodium level did not improve and was at 120 m mmol/L. Further laboratory investigations showed normal thyroid function and normal serum cortisol. His urinary sodium excretion and urine osmolality osmolality were high. [Table 2]. On the basis of the above findings, diagnosis of SIADH was made. His treatment was altered and his fluid intake was restricted to less than 1 liter per day. Following this, serum sodium levels gradually improved to reach 135 mmol/L. [Table 3]

DISCUSSION

The first case report of the SIADH was done by Bartter and Schwartz in October 1957, of two bronchogenic carcinoma patients, who developed significant euvolemic hyponatremia. [1,9] Syndrome of Inappropriate Antidiuresis is diagnosed when euvolemic hyponatremia is present accompanied with low serum osmolality and inappropriately elevated urine osmolality with normal renal, thyroid and adrenal function. [14,15] [Table 1], Syndrome of inappropriate anti-diuresis [SIAD] can be due to either increased release of antidiuretic hormone [independently from effective serum osmolality or circulating volume] from pituitary

Cite this article as: Metwali H, Hasan H, Yousuf M. Pregabalin Induced Syndrome of Inappropriate Anti-Diuretic Hormone (SIADH) Secretion: A Case Report. J Basic Clin Pharma 2019;10: 45-48.

Table 1: Criteria for diagnosing SIADH.

Decreased effective osmolality of the extracellular fluid (Posm <275 mOsmol/kg H_2O).
Inappropriate urinary concentration (Uosm >100 mOsmol/kg H_2O with normal renal function) at some level of plasma hypo-osmolality.
Clinical euvolemia, as defined by the absence of signs of hypovolemia (orthostasis, tachycardia, decreased skin turgor, dry mucous membranes) or hypervolemia (subcutaneous edema, ascites).
Elevated urinary sodium excretion (>20-30 mmol/L) while on normal salt and water intake.
Absence of other potential causes of euvolemic hypo osmolality: severe hypothyroidism, hypocortisolism (glucocorticoid insufficiency).
Normal renal function and absence of diuretic use, particularly thiazide diuretics**.**

SIADH: Syndrome of Inappropriate Antidiuretic Hormone Secretion; H_2O: Water; Kg: Kilogram; Mmol: Millimole; Mosmol: Milliosmole; Posm: Plasma Osmolality; Uosm: Urine Osmolality.

Table 2: Laboratory investigations.

Hyponatremia Work Up:		
Sodium (Serum)	(135-145 mmol/L)	115
Sodium (Urine)	(mmol/L)	77
Urine Osmolality	(250-900 mOsm/kg)	272
Serum Osmolality	(288-298 mOsm/kg)	247
Random Serum Cortisol	(nmol/L)	595
Thyroid Panel:		
Thyroid Stimulating Hormone (TSH)		2.67
	(0.6- 5 mIU/L)	
Free T4	(9-19 pmol/L)	19.21

Table 3: Sodium level and pregabalin administration.

Variables	Sodium Level	Administration of Pregabalin
Baseline	136	Started
At Admission	115	Stopped
Normal Saline 0.9% Infusion	119	Off
Hypertonic Saline 2%	121	
Hypertonic Saline 2%	122	
Fluid Restriction Started	126	
	128	
	133	
	135	

gland or either ectopic sources or unresponsiveness to the secreted antidiuretic hormone due to mutation in V2 receptors in the kidney, which is nephrogenic syndrome of inappropriate anti-diuresis [NSIAD].[16] Antidiuretic hormone [ADH, arginine vasopressin] secretion results in a concentrated urine and therefore a reduced urine volume. The higher the plasma ADH, the more concentrated the urine. In most patients with the syndrome of inappropriate secretion of antidiuretic hormone (SIADH), ingestion of water does not adequately suppress ADH, and the urine remains concentrated. This leads to water retention, which increases TBW. This increase in TBW lowers the plasma sodium concentration by dilution. In addition, the increase in TBW transiently expands the extracellular fluid volume and thereby triggers increased urinary sodium excretion, which both returns the extracellular fluid volume toward normal and further lowers the plasma sodium concentration in general increase ADH secretion or activity impairs the ability of the kidney to dilute urine , resulting in decreased excretion of ingested water and a highly concentrated and decreased urine volume.[17-19]The common causes of syndrome of inappropriate antidiuresis are numerous. Many drugs are known to cause SIADH by mimicking the action of Arginine vasopressin, stimulate its release, or enhance its action. [Tables 3 and 4] Pregabalin is approved to be used in Fibromyalgia, Neuropathic pain associated with diabetic peripheral neuropathy, and spinal cord injury, adjunctive therapy in Partial-onset seizures, and Post-herpetic neuralgia. Pregabalin is a gamma-aminobutyric acid [GABA] analog that strongly binds to the alpha [2]-delta site [a subunit of voltage-gated calcium channels] in CNS tissues. The exact mechanism of action is not fully understood. Binding to the alpha [2]-delta subunit may be involved in pregabalin's effects on neuropathic pain and seizure control. Pregabalin reduces the calcium-dependent release of pro-nociceptive neurotransmitters, possibly by modulation of calcium channel function. Pregabalin may also interact with descending noradrenergic and serotonergic pathways in the brainstem that modulate pain transmission in the spinal. [20] Pregabalin is among the first line pharmacological agents to treat

Table 4: Drug Induced Syndrome of Inappropriate Anti-Diuretic Hormone (SIADH).

Mechanism of Hyponatremia	Examples
Increased hypothalamic production of ADH	Antidepressants Tricyclic antidepressants (amitriptyline, protriptyline, desipramine) Selective serotonin reuptake inhibitors Monoamine oxidase inhibitors Anti-psychotic drugs Phenothiazines (thioridazine, trifluoperazine) Butyrophenones (haloperidol) Antiepileptic drugs Carbamazepine, oxcarbazepine, sodium valproate Anti-cancer agents Vinca alkaloids (vincristine, vinblastine) Platinum compounds (cisplatin, carboplatin) Alkylating agents (intravenous cyclophosphamide, melphalan, ifosfamide) Miscellaneous (methotrexate, interferon, levamisole, pentostatin, monoclonal antibodies) Opiates
Potentiation of ADH effect	Anti-epileptic drugs Carbamazepine, lamotrigine Antidiabetic drugs Chlorpropamide, tolbutamide Anticancer agents Alkylating agents (intravenous cyclophosphamide) Non-steroidal anti-inflammatory drugs

neuropathic pain. Other medications used also to treat neuropathic pain like tricyclic antidepressant [TCA], selective serotonin reuptake inhibitors [SSRI], and selective serotonin norepinephrine reuptake inhibitors [SNRI]. These medications cause SIADH by enhancing the ADH release and we expect that Pregabalin follow the same mechanism of other antidepressants.

CONCLUSION

Hyponatremia is uncommon side effect of pregabalin and there are only a few case reports of pregabalin induced SIADH. Our patient was prescribed Pregabalin for neuropathic pain and developed symptomatic severe hyponatremia a week after taking this medication. His Naranjo Score is 7, which suggests that this is a probable adverse drug reaction. To our knowledge this is the first case report Pregabalin induced SIADH causing hyponatremia in Saudi Arabia. Our aim is to add our case report to the few existing case reports of Pregabalin induced SIADH and increase the awareness among the clinicians and pharmacists about this serious adverse drug effect.

REFERENCES

1. Upadhyay A, Jaber BL, Madias NE. Incidence and prevalence of hyponatremia. Am J Med. 2006;119:30-35.
2. Stelfox HT, Ahmed SB, Khandwala F. The epidemiology of intensive care unit-acquired hyponatraemia and hypernatraemia in medical-surgical intensive care units. Crit Care 2008; 12: R162.
3. Kovesdy CP, Lott EH, Lu JL. Hyponatremia, hypernatremia, and mortality in patients with chronic kidney disease with and without congestive heart failure. Circulation 2012,125:677-74.
4. Miller M, Morley JE, Rubenstein LZ. Hyponatremia in a nursing home population. J Am Geriatr Soc 1995;43:1410-3.
5. Ayus JC, Arieff AI. Postoperative hyponatremia. Ann Intern Med 1997;126:1005-10.
6. Chua M, Hoyle GE, Soiza RL. Prognostic implications of hyponatremia in elderly hospitalized patients. Arch Gerontol Geriatr 2007;45:253-8.
7. Sedlacek M, Schoolwerth AC, Remillard BD. Electrolyte disturbances in the intensive care unit. Semin Dial 2006;19:496-1.
8. Siegel AJ, Baldessarini RJ, Klepser MB, McDonald JC. Primary and drug induced disorders of water homeostasis in psychiatric patients: principles of diagnosis and management. Harv Rev Psychiatry 1998;6:190-0.
9. Bartter FC, Schwartz WB. The syndrome of inappropriate secretion of antidiuretic hormone. Am J Med. 1967;42:790-6.
10. Chan TY. Drug-induced syndrome of inappropriate antidiuretic hormone secretion. Causes, diagnosis and management. Drugs Aging 1997;11:27-4.
11. Izzedine H, Fardet L. Angiotensin-converting enzyme inhibitor-induced syndrome of inappropriate secretion of antidiuretic hormone: case report and review of the literature. Clin Pharmacol Ther 2002; 71:503-7.
12. Jacob S, Spinler SA. Hyponatremia associated with selective serotonin reuptake inhibitors in older adults. Ann Pharmacother 2006;40:1618-2.
13. Spital A. Diuretic-induced hyponatremia. Am J Nephrol 1999;19:447-52.
14. Ellison DH, Berl T. The syndrome of inappropriate anti-diuresis. N Engl J Med. 2007;356(20):2064-72.
15. Palmer BF, Gates JR, Lader M. Causes and management of hyponatremia. Ann Pharmacother. 2003;37:1694-2.
16. Earl H. Rudolph, DO William F. Pendergraft, III, MD, PhD Edgar V. Lerma, MD. Common Electrolyte Disorders: Hyponatremia. Hospital Physician January 2009; 23:32-48.
17. Foote EF: Syndrome of inappropriate antidiuretic hormone secretion and diabetes insipidus. In: Tisdale JE, Millder DA (eds). Drug-induced diseases, prevention detection and management. Bethesda, MD: American Society of Health-System Pharmacists 2005;611-4.
18. Rose BD: Causes of the SIADH. In: Rose BD, ed. UpTo Date [Electronic database]. Waltham, MA, 2007
19. Rose BD, Post TW. Clinical Physiology of Acid-Base and Electrolyte Disorders, 5th edn, McGraw-Hill, New York, USA, 2001. p. 703.
20. Bialer M, Johannessen SI, Kupferberg HJ, et al. Progress report on new antiepileptic drugs: a summary of the fourth Eilat conference (EILAT IV). Epilepsy Res 1999; 34:1-41.