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Syndrome of Inappropriate Anti-diuretic Hormone Secretion and Pregabalin – a Critical Alert on a Potentially Reversible Side-effect

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Abstract:

Syndrome of inappropriate antidiuretic hormone secretion (SIADH) is the commonest cause of euvolemic hyponatremia. Several drugs are known to cause this syndrome. Pregabalin, a drug now used widely for a number of neurologic disorders, may cause hyponatremia secondary to salt wasting nephropathy. However, SIADH induced by pregabalin has been reported very infrequently in the literature. We report a case of hyponatremia in a patient started on pregabalin recently, who fulfilled criteria for SIADH and rapidly reversed on discontinuation of the drug. Awareness of this complication will help the clinician to diagnose and treat new onset hyponatremia in patients started on pregabalin.

Key words: Hyponatremia, Nervous System Diseases, Inappropriate ADH Syndrome, Vasopressins, Humans.

Introduction

Hyponatremia, often defined as serum sodium less than 130 mmol/L, is the most common electrolyte disturbance among hospitalized patients [1,2]. The syndrome of inappropriate anti-diuretic hormone secretion (SIADH), first reported by Bartter and Schwartz in 1967, is the most common cause of euvolemic hyponatremia [3]. Causes of SIADH include malignant diseases (e.g., carcinoma, lymphomas, sarcomas), pulmonary disorders (e.g., pneumonia, asthma), central nervous system disorders (e.g., meningitis, stroke, head trauma), and a number of medications [1]. We report a case of drug induced SIADH due to pregabalin commonly used for neuropathic pain. Although pregabalin induced hyponatremia due to salt wasting nephropathy has been described, SIADH as the underlying mechanism of hyponatremia due to pregabalin has been reported only rarely.

Case Report

A 55-year-old male presented with nausea and hiccups. Two weeks before this he was started on pregabalin 75 mg once daily for his neuropathic pain secondary to L4,L5 radiculopathy. He was neither a diabetic nor a hypertensive. There was no past history of hypothyroidism or coronary artery disease. Apart from pregabalin, he was not on any medications. Physical examination was normal. Clinically he was euvolemic as evidenced

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by absence of pedal edema, a normal jugular venous pressure, clear chest and absence of signs of dehydration. His complete blood counts, blood sugars, urea, creatinine and uric acid were normal. His serum sodium was 108 meq/L and potassium 4.2 meq/L, serum osmolarity 260 mosm. Urinary sodium was 60 meq/L and potassium 80 meq/L and urine osmolarity 280 mosm. His thyroid profile, serum cortisol, chest X-ray, ECG and 2D echocardiogram were normal. Hence criteria for SIADH were fulfilled. Moreover, since he was not on any other medication and had no evidence of infection or malignancy, we presumed that SIADH was secondary to pregabalin. Further evidence for this was obtained by the prompt normalization of sodium within 3 days of discontinuing pregabalin. Patient improved clinically and biochemically after stopping pregabalin. He came for follow up after two weeks and his serum sodium was 132 mmol/L.

Discussion

Hyponatremia is the most frequent electrolyte disorder [1,2] and SIADH accounts for approximately one-third of all cases [3]. Antidiuretic hormone (ADH), also known as Arginine vasopressin (AVP) is secreted from the posterior pituitary gland in response to an increased plasma sodium concentration. It increases cellular permeability to water in the distal tubule and collecting duct of the nephron, leading to water reabsorption by the kidney [4,5].

SIADH is characterized by either a sustained release of ADH in the absence of any stimulus, or by enhanced action of ADH on the kidneys [6]. Increased ADH activity in kidneys impairs ability to dilute urine resulting in decreased excretion of ingested water and a highly concentrated and low volume urine [4,5]. In this setting unrestricted fluid intake leads to hypotonicity of plasma and hyponatremia results. Usually SIADH patients have euvolemic status because excess water gets evenly distributed across all body compartments [5]. The causes of SIADH include malignant disease, pulmonary disorders, central nervous system causes and drugs [1]. Drugs that are commonly implicated to cause SIADH are listed in table 1. In order to diagnose SIADH it is important to ascertain the euvolemic status of the patient, both clinically and by laboratory measurements.

We describe a case of drug induced SIADH due to pregabalin. Pregabalin is an analog of the neurotransmitter gamma-aminobutyric acid that has analgesic, anticonvulsant and anxiolytic properties [7]. It is now widely used for neuropathic pain (diabetic, post herpetic and neuropathy associated with spinal cord injury), adjunctive therapy in partial

Table 1: Drugs commonly causing SIADH

Analgesics	Diclofenac Ibuprofen
Anticonvulsants	Carbamazepine Valproic acid Levetiracetam
Antibiotics	Azithromycin Rifabutin
Psychotropic agents	Chlorpromazine Haloperidol Risperidone Lorazepam SSRI
Antiparkinsonism drugs	Levodopa Trihexyphenidyl Amantadine
Cardiac agents	Amiodarone Enalapril Lisinopril Hydrochlorthiazide
Anticancer agents	Cisplatin Chlorambucil Cyclophosphamide Vinca alkaloids

seizures, anxiety disorders and fibromyalgia. The common side effects of pregabalin are dizziness and somnolence due to central nervous system disturbances [8]. Other dose dependent side effects reported with pregabalin include peripheral edema and weight gain [7,9].

Hyponatremia has been reported as an uncommon side effect of pregabalin. Both salt wasting nephropathy and SIADH have been described, resulting in this infrequent adverse effect [10,11]. Our patient had euvolemic hyponatremia with low serum osmolarity, high urine sodium and normal thyroid function and cortisol, all fitting the criteria for SIADH [1]. Clinical and laboratory features of salt wasting nephropathy and SIADH overlap significantly, distinction being made possible only by euvolemia and improvement with fluid restriction in the latter [12,13]. Our patient had a normal central venous pressure and improved with fluid restriction.

We used the Naranjo algorithm to objectively ascertain that pregabalin resulted in the adverse event in this patient [14]. Drugs induce SIADH by either increasing the sensitivity of the nephron to ADH (chlorpropamide) or augmenting the production of ADH centrally (antipsychotics, antidepressants and vinca alkaloids). Certain drugs like cyclophosphamide and carbamazepine utilize both mechanisms [5]. Since most actions of pregabalin occur via interactions within the central nervous system, it seems logical to hypothesise that pregabalin induces SIADH by increasing the secretion of ADH form the pituitary. However, more case reports and large scale randomized trials are required to test this hypothesis.

Conclusion

SIADH, particularly due to drugs is becoming an increasingly common cause for hyponatremia. Analysis of available literature and our case report indicates that pregabalin may cause hyponatremia by inducing salt wasting nephropathy as well as SIADH. Clinicians must be aware of this possibility since withdrawal of the drug results in rapid correction of hyponatremia due to SIADH.

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