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Syndrome of inappropriate secretion of antidiuretic hormone due to citalopram and venlafaxine

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Abstract

Introduction: Selective serotonin reuptake inhibitors (SSRIs) and venlafaxine are often used to treat depression in the elderly due to their low incidence of side effects. All five of the SSRIs currently available and venlafaxine have been associated with hyponatremia.
Case Report: This article describes the case of an 87-year-old man with depression who presented with hyponatremia after starting treatment with citalopram. After excluding other common causes of hyponatremia, a diagnosis of syndrome of inappropriate secretion of antidiuretic hormone (SIADH) was confirmed. Sodium levels returned to the normal range following discontinuation of citalopram. Subsequently, due to the persistence of depression, treatment with venlafaxine was initiated. Three weeks later, hyponatremia associated with SIADH was once again diagnosed and venlafaxine was discontinued. The hyponatremia resolved in 2 weeks.
Discussion: Both SSRIs and venlafaxine have been associated with SIADH in numerous case reports and retrospective studies. Risk factors for developing hyponatremia with these drugs are advanced age and treatment with other medications. To our knowledge, this is the first case report in which SIADH was associated with two different families of antidepressants in the same patient.
Conclusion: Physicians should be aware of the risk of hyponatremia when prescribing SSRIs and venlafaxine in elderly patients with multiple drug therapies. Sodium levels should be monitored during treatment.

Keywords: Hyponatremia; Elderly; SSRIs; Venlafaxine; SIADH

1. Introduction

Selective serotonin reuptake inhibitors (SSRIs) are often used to treat depression in the elderly due to their favorable side-effect profile and relative safety in case of overdose. However, all six SSRIs currently available to treat depression (fluoxetine, sertraline, paroxetine, fluvoxamine, citalopram and escitalopram) have been associated with hyponatremia [1,2]. Venlafaxine, a serotonin and noradrenaline reuptake inhibitor with a mechanism of action similar to that of SSRIs at low doses, has also been reported to cause hyponatremia [3]. One of the most common causes of hyponatremia is syndrome of inappropriate secretion of antidiuretic hormone (SIADH). Diagnostic criteria for SIADH include the following: hypotonic hyponatremia; less than maximally dilute urine (U_{osm} usually >100 mOsm/kg); urinary sodium loss (usually >20 mEq/L); clinical euvolemia; and normal renal, adrenal and thyroid functions [4]. Stress, medications [5] and medical conditions, such as tumors (notably oat cell carcinoma of the bronchus), stroke and adrenal insufficiency, can precipitate SIADH in the elderly.

Symptoms of hyponatremia are extremely variable and are associated with the rapidity of the decrease in serum sodium levels. Whereas patients with an acute and precipitous decrease in serum sodium levels often present with telltale signs and symptoms such as ataxia, delirium, confusion and seizures, patients with chronic mild hyponatremia can be asymptomatic or can present with nonspecific symptoms of fatigue, lethargy and anorexia, which are also symptoms of depression. This is problematic because

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hyponatremia induced by SSRIs evolves slowly, often resulting in the misattribution of symptoms of hyponatremia to depression or to worsening of underlying medical conditions [1]. Multiple medical problems confer an increased risk for depression among the elderly, and the same medical problems confer an increased risk for SIADH among patients treated with SSRIs [1]. As such, it is important for clinicians to be aware of the clinical features associated with SSRI-induced SIADH in the elderly.

2. Case report

An 87-year-old man was admitted to a university-affiliated hospital with a plasma sodium concentration of 119 mEq/L (normal range: 135–145 mEq/L), which was identified through a routine blood test carried out by his general practitioner.

The patient's past medical history included the following: hypertension, ischemic heart disease, hyperuricemia, prostatic syndrome, chronic glaucoma, hiatus hernia, tuberculosis, dyslipidemia and depression. The only clinical symptoms presented on admission were asthenia and weight loss. Abnormal neurological signs were absent, and mental status was intact. One week prior to admission, treatment with citalopram, 20 mg/day, had been initiated for depression. Other medications taken at the time of admission included the following: losartan, 25 mg/day; omeprazole, 20 mg/day; allopurinol, 150 mg/day; clopidrogel, 75 mg/day; carvedilol, 12.5 mg, bid; simvastatin, 20 mg/day; isosorbide mononitrate, 40 mg, tid; 0.5% timolol ophthalmic drops, 1 drop, bid; tebetane (phytosterol used to treat prostatic syndrome), 1 tablet/day; alprazolam, 0.25 mg, bid.

On physical examination, blood pressure, temperature and heart rate were within normal limits. The patient was euvolemic (no postural changes in blood pressure or heart rate). Cardiac, pulmonary and abdominal examinations revealed normal results. No evidence of central or peripheral nervous system dysfunction was found.

Results of blood and urine analyses on admission are shown in Table 1. Serum osmolality was decreased (259 mOsm/kg) relative to urine osmolality (463 mOsm/kg), and urine sodium (46 mEq/L) was elevated. Based on these findings, a diagnosis of SIADH was hypothesized.

Several tests were performed in order to identify the cause of SIADH. Hepatic, hematologic, adrenal and thyroid indices were all within normal ranges. Tumor screening markers also yielded negative results. Chest X-rays revealed the presence of slight cardiomegaly, while computed tomography scans of the brain, chest and abdomen yielded normal results. After ruling out other causes of SIADH, a diagnosis of SIADH associated with citalopram was presumed. Citalopram was discontinued on admission, and fluid intake was restricted. The patient responded favorably; 1 month later, the serum sodium concentration was 132 mEq/L.

Two months later, the patient returned to the hospital outpatient clinic with persistent symptoms of depression.

Table 1
Blood and urine test on admission

Laboratory test	First admission (September 9, 2003)	Second admission (December 1, 2003)	Normal range
Serum sodium (mEq/L)	119	126	135–145
Serum potassium (mEq/L)	5	4.4	3.5–5.0
Serum osmolality (mOsm/kg)	259	269	280–310
Urine osmolality (mOsm/kg)	463	729	<150
Urine sodium (mEq/L)	46	55	20–40

Treatment with venlafaxine, 75 mg/day, was initiated, with careful monitoring of electrolytes. It should be noted that, when used in low doses such as 75 mg/day, venlafaxine demonstrates minimal noradrenaline reuptake inhibition, functioning predominantly as other SSRIs. Three weeks later, laboratory tests detected a serum sodium concentration of 126 mEq/L. Although the patient remained asymptomatic, he was readmitted for observation. The results of laboratory analysis obtained on readmission are presented in Table 1. A diagnosis of SIADH was once again established, and the most probable cause of this was hypothesized to be venlafaxine. Venlafaxine was thus discontinued and, 2 weeks later, the serum sodium concentration returned to normal (136 mEq/L) and remained at the same level through 1 month of follow-up.

3. Discussion

To our knowledge, this is the first case report in which SIADH was associated with two different classes of antidepressants in the same patient.

Several case reports have implicated SSRIs as potential causes of SIADH. Fluoxetine-associated SIADH was first reported following its introduction in the United States [6]. Since then, cases of hyponatremia associated with all SSRIs, as well as with venlafaxine, have been described [7–9].

Two reviews have analyzed a series of case reports of SIADH associated with the use of SSRIs. Liu et al. [7] reviewed a total of 736 cases and found that fluoxetine was involved in 554 (75.3%) cases, paroxetine was involved in 91 (12.4%) cases, sertraline was involved in 86 (11.7%) cases and fluvoxamine was involved in 11 (1.5%) cases. The average time to onset of hyponatremia after initiating treatment was 13 days (range, 3–120 days), and >70% of the cases involved patients aged ≥65 years. In all cases, the patient's condition returned to normal 2–28 days after the discontinuation of SSRIs. No association between SSRI dosage and the time of onset or the severity of hyponatremia was found. Kirchner et al. [10] reviewed a total of 46 published case reports and 202 cases reported by the Committee on Safety of Medicines. Both reviews reported similar results: the mean age of the patients was 78±8 years, the time to detection was 21–22 days, the serum sodium level

was 118.0 mmol/L and the mean time to normalization of serum sodium upon cessation of SSRI was 10 days. The dose of SSRIs was greater than recommended in 6% of published cases and in 15% of cases reported by the Committee on Safety of Medicines. The majority of cases in published cases were female (74–80%). The most common symptoms reported in published cases (29 of 46) were confusion, weakness, lethargy and drowsiness.

Bouman et al. [11], in a retrospective chart review of 32 elderly patients taking SSRIs, found that eight patients (25%) developed hyponatremia. Four of them developed symptomatic hyponatremia, and SIADH was confirmed by laboratory tests. In cases in which hyponatremia was mild (130–135 mmol/L) and associated with diuretic use or comorbid physical illnesses, SIADH laboratory tests were not performed and, thus, SIADH was not confirmed. The limitations of this study were a small sample size and its retrospective design, with incomplete data in some cases.

Movig et al. [12] conducted a 2-year epidemiological study using a case–control design and analyzed the differences between cases ($n=29$) with hyponatremia (Na <130 mmol/L) during treatment with antidepressant medication versus controls ($n=78$) with a normal serum concentration (136–144 mmol/L) during treatment with antidepressant medication. Current use of SSRIs was found among 76% of cases and among 49% of controls [unadjusted odds ratio (OR)=3.3]. Age was a potential confounder in this study, as the mean age among cases was greater than that among controls (68 vs. 57 years). There was a synergistic effect to developing hyponatremia with the concurrent use of SSRIs and diuretics compared with nonuse. Furthermore, this effect (SSRI+diuretics) was more pronounced in elderly patients (age ≥65 years), who showed the highest risk (OR=13.5) of developing hyponatremia.

In a retrospective controlled study [3] of inpatients treated in a psychogeriatric unit, a study group ($n=74$) receiving treatment with an SSRI or venlafaxine was compared with a control group ($n=125$) not receiving an SSRI or venlafaxine within 3 months of sodium testing. The groups were not significantly different in terms of age, gender or type of medical illness. Thirty-nine percent of study group patients were hyponatremic (sodium <135 mmol/L) versus 10% of control group patients. (OR=5.6). Hyponatremia was significantly more common among subjects treated with venlafaxine (71%) than among subjects treated with paroxetine (32%) or sertraline (29%), which may explain the somewhat higher OR for SIADH among antidepressant-treated subjects in this study as compared to studies that did not examine venlafaxine. Concomitant diuretic use (primarily thiazides) was associated with an increased risk of SIADH, convergent with previous findings, whereas female gender was not significantly associated with SIADH.

Fabian et al. [13] prospectively investigated the incidence of paroxetine-induced hyponatremia in 75 elderly patients (63–90 years old) diagnosed with a major depressive episode. Plasma sodium levels were drawn before initiating paroxetine therapy and after 1, 2, 4, 6 and 12 weeks of treatment. Hyponatremia developed in 9 (12%) of 75 patients after initiation of paroxetine treatment, and the mean time to the development of hyponatremia after starting paroxetine was 9.3 ± 4.7 days.

In summary, there is a growing body of evidence suggesting that SSRIs and venlafaxine are associated with hyponatremia. Moreover, several factors have been associated with an increased risk of SIADH among persons treated with these medications, including older age, female gender, comorbid medical conditions and concomitant treatment with diuretics. Concomitant use of antihypertensives and diuretics may increase the risk of SSRI-associated hyponatremia. This may be explained by the fact that the addition of paroxetine, fluoxetine and fluvoxamine can result in increased serum concentrations of several diuretics through inhibition of CYP450 hepatic enzymes.

Although there is no apparent correlation between dose of SSRI and SIADH, previous studies have not examined the association between SIADH and plasma levels of antidepressants. In the case discussed above, the patient was taking omeprazole, a potent inhibitor of cytochrome *P*450-2C19 of which citalopram is a substrate. The serum level of citalopram may have been unexpectedly high, and this may have contributed to the development of SIADH.

In this case report, there was a short latency of onset of hyponatremia (7–21 days) following the initiation of treatment with citalopram and venlafaxine. This finding converges with those of previous studies [7,10,13] that have reported short time intervals between initiation of SSRI and onset of hyponatremia (9–20 days). However, there is also evidence that the onset of SIADH can occur as much as 16 months following the initiation of SSRI treatment [14]. This underscores the importance of monitoring plasma sodium concentration longitudinally during the course of antidepressant treatment among the elderly, particularly among patients with the risk factors described above.

4. Conclusion

Physicians should be aware of the possibility of SSRI-associated and venlafaxine-associated hyponatremia in elderly patients. Physicians should also be aware that, unlike obvious manifestations of acute hyponatremia, the insidious onset of hyponatremia that is common in the elderly may present with nonspecific symptoms that overlap with those of depression. Routine monitoring is indicated in patients with risk factors in receiving SSRIs or venlafaxine. Prospective studies should be undertaken in order to further delineate and characterize risk factors for SIADH among elderly patients treated with these medications.

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