Case Report

Escitalopram-Induced Chronic Euvolemic Hyponatremia

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Abstract

Selective serotonin reuptake inhibitors (SSRIs), through the recent years have seen an increase in the number of prescriptions for a spectrum of mood disorders, especially in the geriatric population. Despite being a well-tolerated antidepressant, SSRIs have been associated with hyponatremia, a rare, but fatal adverse effect and the incidence ranges from 0.5%–32% in literature. Euvolemic hyponatremia is most commonly associated with syndrome of inappropriate secretion of antidiuretic hormone. An extensive review of literature was carried out, and we came across a total of 20 cases where escitalopram was reported as the causative agent of hyponatremia. We report a case of an 82-year-old female patient who had a history of acute onset, progressive memory impairment, and behavioral changes with depressive cognition precipitated by the death of her husband, for which she was treated with escitalopram 5 mg/day and clonazepam 0.5 mg/day. She was admitted to the hospital with presenting complaints of gait imbalance, tremors, irritability, confusion, decreased speech output and persecutory delusions. She was diagnosed with late-onset organic psychosis, precipitated and worsened by escitalopram-induced chronic uncontrolled euvolemic hyponatremia, with a sodium level of 115 mmol/L. On discontinuation of escitalopram, the patient's serum sodium level improved gradually, and her consciousness became better. This is the second case with recurrent hyponatremia in the literature up to this date, with the other being reported by Tsai *et al.*, in 2012. Furthermore, the dose of escitalopram was only 5 mg/day compared to other reported cases where the dose ranged between 10–20 mg/day.

Keywords: Escitalopram, hyponatremia, late-onset organic psychosis, selective serotonin reuptake inhibitor, syndrome of inappropriate secretion of antidiuretic hormone

Introduction

Escitalopram, one of the newest additions to the Selective serotonin reuptake inhibitors (SSRIs), is a pure S-enantiomer of racemic citalopram and is the most selective among the SSRIs. Escitalopram is the mainstay pharmacotherapy for depressive disorders in the elderly due to their wider safety margin.[1-3] Hyponatremia, where the serum sodium concentration falls below 135 mEq/L, is a rare, but potentially fatal complication of SSRI therapy can be present as asymptomatic in chronic hyponatremia patients or with symptoms ranging from mild loss of appetite, nausea, vomiting, headache, easy fatiguability to severe altered sensorium, agitation, coma, and even death. Case-control studies and further literature review suggests higher incidences of hyponatremia with fluoxetine citalopram, paroxetine, fluvoxamine, and sertraline.[4] Escitalopram as the indicative drug for hyponatremia is reported much less compared to other SSRIs. The mechanism of action is hypothesized to be syndrome of inappropriate secretion of antidiuretic hormone.[5,6] SSRIs, the so-called second generation of antidepressants, are the selective and potent inhibitors of Na^+/K^+ adenosine triphosphatase (ATPase)-dependent serotonin transporter (SERT, belonging to SLC6 gene family) at the presynaptic axon terminal, thereby inhibiting the reuptake of serotonin from the synaptic cleft so that serotonergic neurotransmission is extended for a long period. SSRIs are currently used as the first-line pharmacotherapy for major depressive disorder (especially in the elderly population), and a spectrum of other mood disorders such as anxiety disorders, obsessive-compulsive disorder, bulimia nervosa, panic disorder, premenstrual dysphoric disorder, posttraumatic stress disorder, bipolar, and treatment-resistant depression. SSRIs are also used for other off-label uses including, but not limited

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to fibromyalgia, autism, and vasomotor symptoms caused by menopause and Raynaud's phenomenon.[7] SSRIs became the choice of drugs for the treatment of depressive disorders in the elderly as they showed dramatic response to the treatment, and have little or no side effects such as constipation, dry mouth, sedation, and cardiovascular side effects associated with the older tricyclic antidepressants, and monoamine inhibitors such as tachycardia and orthostatic hypotension. SSRIs are well-tolerated in the patients with side effects ranging from mild nausea to more severe adverse effects such as sexual dysfunction, gastrointestinal adverse effects such as nausea, vomiting, anorexia, dyspepsia, flatulence, cardiovascular effects such as QT_c prolongation, and other adverse effects such as headache, anxiety, insomnia, somnolence, emotional blunting, and seizures.[7-9]

Here, we report a case of chronic uncontrolled euvolemic hyponatremia associated with escitalopram. Our case report highlights the second escitalopram-induced chronic hyponatremia, which was first reported by Tsai *et al*., in 2012.[10]

Case Report

An 82-year-old female patient J, admitted in Indo American Hospital, Vaikom, Kerala, started showing symptoms of progressive memory impairment and behavioral changes, which were acute in onset, following the death of her husband. She was a hypertensive patient for the past 30 years and was taking amlodipine 5 mg daily. She also had Type 2 Diabetes Mellitus, which was managed by diet restrictions. She started showing symptoms of depression in the following months with sudden crying spells, depressive thoughts, suicidal ideation, and sleep impairments. Her depressive cognition was treated with escitalopram 5 mg/day and clonazepam 0.5 mg/day. This was continued for the next 2 months, during which she started showing an exacerbation of symptoms. She had gait imbalance while getting up and moving around, tremors, restlessness, persecutory delusions, decreased speech output, and significant memory impairment. She was admitted to the hospital for altered mental status presenting with delirium.

On admission, her BP was 140/80 mmHg with a pulse rate of 120 BPM. She was oriented in person, but not in time, date, and place. Her speech output was decreased. On examination, she was bradykinetic with rigidity, slow, and ataxic. Her renal, thyroid, and liver function tests were normal. Lumbar puncture cerebrospinal fluid study and autoimmune panel came out as normal. Her brain magnetic resonance imaging gave the impression of few white matter ischemic changes in bilateral cerebral hemispheres. The urine culture test showed the growth of *Escherichia coli* and mild pyuria despite the patient being afebrile. She was euvolemic with a serum sodium concentration of 118 mmol/L and other laboratory parameters given in Table 1. Escitalopram was discontinued and low-dose tolvaptan at 7.5 mg/day was initiated to correct hyponatremia. Mirtazapine 7.5 mg/day was used to replace escitalopram to manage the signs and symptoms. She was also given norfloxacin 400 mg/day to treat UTI. Over the course of the next few days, the laboratory investigations showed gradual increase in sodium levels along with the resolution of hyponatremic symptoms. At the same time, the features of psychosis became more prominent. Hence, another psychiatric opinion was also taken, after which she was diagnosed with late-onset organic psychosis precipitated and worsened by the chronic uncontrolled euvolemic hyponatremia caused due to the administration of escitalopram. Further, the antipsychotics were adjusted with quetiapine 25 mg/day, risperidone 1 mg/day, and trihexyphenidyl 1 mg/day. The patient was discharged with tolvaptan 7.5 mg/day, mirtazapine 7.5 mg/day, quetiapine 25 mg/day, risperidone, and trihexyphenidyl 1 mg/day.

Table 1: Laboratory investigations

Laboratory test	Levels	Reference range
Serum sodium (mmol/L)	118	135-145
Serum potassium (mEq/L)	4.6	3.5-5.5
Serum creatinine (mg/dl)	1.1	0.6-1.3
Hemoglobin (g/dl)	12.8	12-16
TSH (uIU/ml)	5.12	0.35-5.50
Anti-thyroid peroxidase antibody (U/ml)	<28	0-60

TSH=Thyroid stimulating hormone

Discussion

Chronic escitalopram-induced hyponatremia is a very unusual. The elderly population is at an increased risk of developing hyponatremia compared to others. The risk is high in the first few weeks of treatment, with a median time of onset of 11 days but can occur even after 3 months. Risk further increases with age, female gender, low body weight, other concomitant illnesses such as chronic kidney disease or CHF, polypharmacy, use of diuretics, narcotics, oral hypoglycemic drugs, antipsychotics, higher dose of SSRIs, low serum potassium, and low baseline serum sodium concentrations.[7,10] This patient developed hyponatremia at a low dose of 5 mg/day, which is atypical when compared to other reported cases in literature, in which, the doses varied from 10 to 20 mg/day. In this case, there was a temporal relationship between escitalopram and hyponatremia. Moreover, the patient also had multiple risk factors as mentioned above. The patient had a causality score of 7 on the Naranjo probability scale and the causality was probable for the ADR.

In most scenarios, hyponatremia induced by escitalopram can be reversed by discontinuing escitalopram. Further, in euvolemic hyponatremia, fluid restriction of <1 L/day and in severe symptomatic cases, 3% normal saline, and drugs such as loop diuretics (furosemide), V_2 receptor antagonists (tolvaptan and conivaptan). Hyponatremia is corrected slowly to avoid serious neurological problems such as osmotic demyelination syndrome. The patient is closely monitored during the treatment period to avoid any such complications.

Escitalopram, being a comparatively safer antidepressant can precipitate hyponatremia in low doses as well in the elderly population who will also be present with other multiple risk factors. It is important to identify the risks while prescribing escitalopram in the elderly population and take measures to prevent hyponatremia. A baseline sodium level can be measured before therapy initiation with weekly or bi-weekly measurements of sodium concentrations 1st month. A patient who has developed hyponatremia once should avoid a rechallenge with the same to avoid the risk of developing a more severe hyponatremia. Instead, the patient can be treated with an alternate drug such as mirtazapine, which is less likely to cause hyponatremia compared to SSRI. A clinician can always instruct the patient and his/her family to measure the serum sodium concentrations in any unexplainable emergencies or when the neuropsychiatric symptoms worsen during SSRI therapy.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient (s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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