Duloxetine Induced Hyponatremia

Ebru ŞAHAN[1], Fatma Büşra PARLAKKAYA YILDIZ[2]

SUMMARY

Hyponatremia can be asymptomatic or have a wide range of clinical presentations such as headaches, muscle cramps, nausea, seizures, coma, cerebral edema and may even result in death. Despite it has been suggested that duloxetine has a relatively less risk of hyponatraemia, the number of case reports are increasing. A 45- year old female patient with complaints of fear, anxiety, sleeplessness and headache was started on duloxetine (30 mg/day). In the first week of the treatment, she was admitted to the emergency service with dizziness, dry mouth, polyuria and polydipsia. She had to be transferred to the intensive care unit because of agitation, loss of consciousness and a generalized tonic-clonic seizure. Blood levels of Sodium (Na+), Potassium (K+) and Chlorine (Cl-) were, respectfully, 121 mmol/L, 2.7 mmol/L and 87 mmol/L. Brain imaging displayed cerebral edema. Electrolyte levels were regulated with saline infusions. Amitriptyline was initiated for the ongoing headache and anxiety. In outpatient visits, hyponatremia did not recur in the following 3 months.

Low dose duloxetine was associated with severe hyponatremia signs and symptoms in an individual who was not previously considered as high risk for hyponatraemia. The patient's history did not reveal any complaints related to hyponatremia when she was treated with sertraline two years ago. Based on these, we discussed the risk factors for hyponatremia and risky antidepressant classes.

Keywords: Antidepressants, hyponatremia, inappropriate ADH secretion

INTRODUCTION

Duloxetine is a selective serotonin and noradrenaline reuptake inhibitor. It is used in the treatment of different diseases such as major depressive disorder, fibromyalgia, diabetic neuropathy and anxiety disorders (Augendre-Ferrante et al. 2014, Masuda et al. 2013). It begins to be absorbed 2 hours after oral ingestion, reaching its plasma maximum concentration in approximately 6 hours and has a half-life of 12 hours (Westanmo et al. 2005). Duloxetine doses generally used in trials have been in the 40 -120 mg /day range (Nemeroff et al. 2002). It is often started at a dose of 30 mg/day and can be increased up to a maximum of 120 mg/day dependent upon the response given to the drug.

The most frequently observed side effects of duloxetine are nausea (20%), dry mouth (16%), fatigue (11%), dizziness (11%), constipation (11%), somnolence (8%), decreased appetite (6%) and sweating (5%) (Krüger and Lindstaedt 2007). Cases of hyponatremia following duloxetine use have been reported in elderly patients with depression and neuropathic pain (Choi et al. 2012, Dirks and van Hyfte 2007, Harter et al. 2008, Krüger and Lindstaedt 2007, Li et al. 2012, Mussig et al. 2009, Safdieh and Rudominer 2006). Hyponatremia is defined as a plasma sodium (Na+) concentration of less than 135 mmol/L. Hyponatremia can be asymptomatic or have a wide range of clinical presentations such as headache, muscle cramps, nausea, seizures, coma, cerebral edema and may even result in death (De Picker et al. 2014). Development of hyponatremia following antidepressant medication is mostly hypotonic (dilutional) hyponatremia, that is, the decrease of Na^+ concentration due to increased water volume, the underlying cause is frequently the increase of plasma Anti-Diuretic Hormone (ADH) level (Krüger and Lindstaedt 2007). The relationship of selective

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[1]MD, [2]Assist., Bezmialem Vakıf University, Department of Psychiatry, İstanbul, Turkey.

e-mail: *ebrushaan@hotmail.com*

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serotonin reuptake inhibitor (SSRI) and the serotonin and noradrenaline reuptake inhibitor (SNRI) drugs with ADH has not yet been fully understood (Kulkarni 2015). A multifactorial mechanism underlies the Syndrome of inappropriate ADH secretion (SIADH) resulting from the use of SSRIs or SNRIs, and including induction of ADH secretion by serotonergic and noradrenergic stimulation increasing the effectiveness of ADH in the renal medulla, decreasing the stimulation threshold of osmostat regulating ADH release and the interactions with other medications used (Amoako et al. 2015, Krüger and Lindstaedt 2007). In this article, a case with hyponatremia and associated cerebral edema induced by duloxetine use is presented, the risk factors are reviewed and the drugs of choice after the treatment of hyponatremia are discussed.

CASE

A 45-year old female patient consulted the neurology outpatient clinic with complaints of fear, anxiety, difficulty in falling asleep, fear of death, and severe headache and nausea triggered by upsetting events. The patient was using ramipril, an angiotensin converting enzyme inhibitor (ACEI), after diagnosis of hypertension. History taking revealed that 2 years previously she had been on sertraline for 6 months with similar complaints and had stopped taking the drug after her complaints had regressed. Her neurological examination was unremarkable. Brain computerized tomography did not indicate any abnormal finding and the patient was prescribed duloxetine (30 mg/day) after the diagnosis of migraine and anxiety disorder by the neurologist. Her headache increased, and complaints of dizziness, dry mouth, polyuria, and polydipsia started within the first week of taking the medication. The patient was admitted to the emergency service with added symptoms of blood shot eyes, and numbness of her whole body. She was taken to the intensive care unit after having a generalized tonic-clonic seizure, blurring of consciousness, agitation and deterioration in orientation. Her blood tests results comprised Sodium (Na) 121 mmol/L, Potassium (K) 2.7 mmol/L, Chlorine (Cl) 87 mmol/L, Blood Urea Nitrogen (BUN) 5.61 mg/dl, Creatinine 0.64 mg/dL and Glucose 167 mg/dl. Plasma osmolarity (calculated using the equation (2xNa+Glu / 18 + BUN / 2.8) was 271 mOsm/L (280-290 mOsm/L), urine Na was 74 mmol/L, urine density was 1007. Urine osmolarity which was calculated on the equation [(Density-1000) x40] was found to be 280 mOsm/kg. Hemogram, renal function tests and thyroid function tests were within normal limits. Her blood pressure was 170/90 mmHg and the other system examinations were normal. Brain magnetic resonance imaging (MRI) was evaluated as cerebral edema and ventricular dilatation was observed. According to the physical examination and laboratory results, hypothyroidism, acute or chronic renal failure, adrenal insufficiency and gastroenteritis were excluded. Duloxetine was discontinued, daily fluid intake was restricted and electrolyte treatment was started with saline infusion. After six days in the intensive care unit and two weeks in the internal medicine inpatient clinic, the patient was discharged with only antihypertensive drug, ramipril. She referred back for the cause of her headache and other initial complaints. Renewed blood tests and brain computed tomography showed no abnormal findings. Amitriptyline 10 mg/day was prescribed for migraine and anxiety disorder. Amitriptyline and ramipril were used in the outpatient clinical follow-ups and the recurrence of hyponatremia was not observed till her last visit of the third month.

DISCUSSION

A well-known side effect of SSRIs is syndrome of inappropriate ADH secretion (SIADH). Some criteria have been defined to diagnose SIADH, including presence of euvolemic hyponatremia, plasma osmolarity below 275 mOsm/L, urine osmolarity above 100 mOsm/kg, urinary Na over 40 mEq/L, and BUN below 10 mg/dL. Acid-base balance, adrenal, hepatic, renal and thyroid functions are normal in SIADH (Reddy and Mooradian 2009).

In the literature, there are many cases about the development of SIADH after SSRI and venlafaxine use (De Picker et al. 2014). Among the SSRI medications group, escitalopram has been reported especially to cause SIADH more often, while sertraline and paroxetine are more reliable compared to other SSRIs (Choi et al. 2012). Tricyclic antidepressants, duloxetine, bupropion, reboxetine cause very rarely but possibly to the emergence of hyponatremia (De Picker et al. 2014). De Picker et al. (2014) who compared hyponatremia cases according to drug classes and reported that duloxetine users were very few (1% of the patients examined) in their patient populations, because of the low prescribing rate, and warned readers to be careful in interpreting the low 11% incidence of hyponatremia. In a pharmacovigilance study conducted in France between 2011 and 2013 based on the national health insurance data, the incidence of hyponatremia associated with SSRI and SNRI was compared and the incidence of hyponatremia with duloxetine was found to be higher than that with SSRIs and venlafaxine (Revol et al. 2017). Wider scale studies should be conducted to verify or disprove the conflicting hyponatremia risk rates associated with duloxetine use. Among patients intended to be treated with an antidepressant, especially the old age patients of female gender, low body weight, using other medications such as thiazide diuretics, ACEI, laxatives and such which may cause hyponatremia, with a history of hyponatremia and low basal sodium before the drug use are considered as individuals with

the risk of developing drug-induced hyponatremia (De Picker et al. 2014). When the case reports of SIADH after the use of duloxetine are examined, it is noticed that hyponatremia and SIADH have developed in elderly female patients, within 2-3 days after starting 60-90 mg/day duloxetine (Boumanet al. 1998).

Our patient discussed here was in the middle age group, her weight was within normal limits, she had no additional diagnosis and treatment other than hypertension, and her basal sodium level was above 138 mmol/L; indicating that she was not in the high-risk group. The risk factors for the development of hyponatremia with the use of an antidepressant in this patient were being a female and the use of ramipril (5 mg/day), having been diagnosed with hypertension. After initiation of duloxetine at the low dose of 30 mg/day, severe neurological symptoms, cerebral edema within days and severe, life-threatening clinical state that required follow-up in intensive care unit was observed. A strong, positive correlation between the drug dose and the development of hyponatremia cannot be suggested, and as such the same positive correlation may not be indicated between the amount of decrease in plasma Na^+ level and the severity of the clinical findings of hyponatremia. However, the rapid decrease in the level of Na^+ from baseline may imply a more severe clinical state. Although it is known that SSRIs are more risky for hyponatremia, it is noteworthy that the patient did not have any signs of hyponatremia during the period of sertraline use earlier. In reference to reviews, it has been suggested that mirtazapine, tricyclic antidepressants or bupropion use is safer in patients with depression who have a high risk for hyponatremia (De Picker et al. 2014). Since migraine-related headache, anxiety and insomnia were detected together in our patient, a tricyclic antidepressant, amitriptyline (10 mg /day) was prescribed which could be considered as less risky for hyponatremia development. There are some studies suggesting that low dose amitriptyline is effective in the treatment of migraine; and as a consequence of mild side effects, compliance with and longer duration of drug therapy is facilitated (Doyle Strauss et al. 2016, Gomersall and Stuart 1973, Lampl 2009, Nagata 2009). Duloxetine dose was not increased owing to the patient's adequate response to the 10 mg/day dose. In some studies on patients with mild hyponatremia, continuation of the medication and imposing only fluid restriction significantly improve the hyponatraemia. This resulted in the consideration that drug-induced hyponatremia could be a temporary condition (De Picker et al. 2014,Viramontes et al. 2016).

In conclusion, testing the plasma Na^+ level before and 2 weeks after the start of antidepressant treatment, not in all cases but just the ones in whom hyponatraemia might be considered as risky, could help us in conducting a safer treatment.

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