

Duloxetine-induced Hyponatremia in the Elderly

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ABSTRACT

Hyponatremia and syndrome of inappropriate secretion of antidiuretic hormone (SIADH) are recognized as serious side effects of selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs). As elderly patients are easily predisposed to hyponatremia due to multiple factors, the use of SSRIs or SNRIs may be more likely to aggravate hyponatremia. We report the case of an elderly patient who developed hyponatremia most likely related to SIADH induced by duloxetine, an SNRI. Symptoms of hyponatremia emerged after treatment initiation and resolved with conservative care following discontinuation of duloxetine. Severe hyponatremia, serum hypoosmolality, urine osmolality, and measurable levels of plasma antidiuretic hormone suggested SIADH. Multiple factors, such as physical comorbidities and conditions, and drug interactions, might be associated with hyponatremia. Older patients receiving SNRIs or SSRIs should be closely monitored for clinical and laboratory evidence of hyponatremia.

Keywords: *syndrome of inappropriate secretion of antidiuretic hormone (SIADH), selective serotonin reuptake inhibitor (SSRI), serotonin norepinephrine reuptake inhibitor (SNRI), duloxetine, hyponatremia*

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INTRODUCTION

Both selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs) are rapidly becoming first-line therapeutic medications for depression in older patients, as in younger patients. Duloxetine is classified as a relatively new type of SNRI and is widely used worldwide for a number of indications (diabetic neuropathy, fibromyalgia, urinary stress incontinence) in addition to major depressive disorders. On the other hand, hyponatremia and syndrome of inappropriate secretion of antidiuretic hormone (SIADH) are recognized as serious side effects of SSRIs and SNRIs [1]. As elderly patients are predisposed to hyponatremia

due to medical comorbidities, concomitant drugs, and advanced age by itself, the use of an SSRI or SNRI in the elderly is more likely to aggravate hyponatremia [2, 3]. Here, we describe an older patient who developed severe hyponatremia most likely related to SIADH caused by duloxetine, an SNRI, but was successfully treated by discontinuation of the serotonergic antidepressant and water restriction with salt intake.

CASE REPORT

A 79-year-old female 158 centimeters in height weighing 62 kilograms was referred from her primary care physician and hospitalized because

of a variety of depressive symptoms. She had a medical history of hypertension, hyperlipidemia, and obsolete pulmonary tuberculosis. Her daily medication prior to admission consisted of benidipine hydrochloride 4 mg, valsartan 80 mg, quetiapine 25 mg, and ramelteon 8 mg. Laboratory findings on admission included low levels of serum sodium (131 mEq/L) and chloride (94 mEq/L) and a high level of fasting glucose (121 mg/dL), accompanied by HbA1C 6.2%. A chest radiograph and computed tomograms of the brain, chest and abdomen were all normal except for mild frontal lobe brain atrophy and small calcifications in both upper lung fields. On the day after admission, quetiapine use was discontinued because of glucose intolerance, and treatment with duloxetine 20 mg and clonazepam 0.5 mg per day was initiated for symptoms of anxiety and depression. Her other medications were left unchanged. A week after duloxetine treatment initiation, she began to complain of severe headaches and appetite loss. The duloxetine dose was increased to 40 mg per day by a psychiatrist because it was thought that these physical complaints might be psychiatric symp-

toms. Two days later, the patient experienced a loss of consciousness, and a laboratory test performed 10 days after duloxetine treatment initiation revealed low levels of serum sodium (118 mEq/L) and chloride (83 mEq/L), serum osmolality (240 mOsm/kgH₂O [normal is 275 to 290]), low urine sodium (19 mEq/L) and urine osmolality (123 mOsm/kgH₂O [normal is 50 to 1300]). As duloxetine-related SIADH was suggested, duloxetine treatment was discontinued but treatment with the patient's other medications was continued. The plasma ADH concentration was subsequently found to be within the normal range (0.5 pg/mL), and the patient had normal thyroid and adrenal function. Following intravenous sodium replacement therapy and improvement in the patient's hyponatremia, the patient did not complain of severe headaches or abdominal symptoms, and there were no changes in her body weight. The serum sodium concentration normalized 5 days after the discontinuation of duloxetine (Fig. 1), and subsequently remained within the normal range without replacement of saline intake.

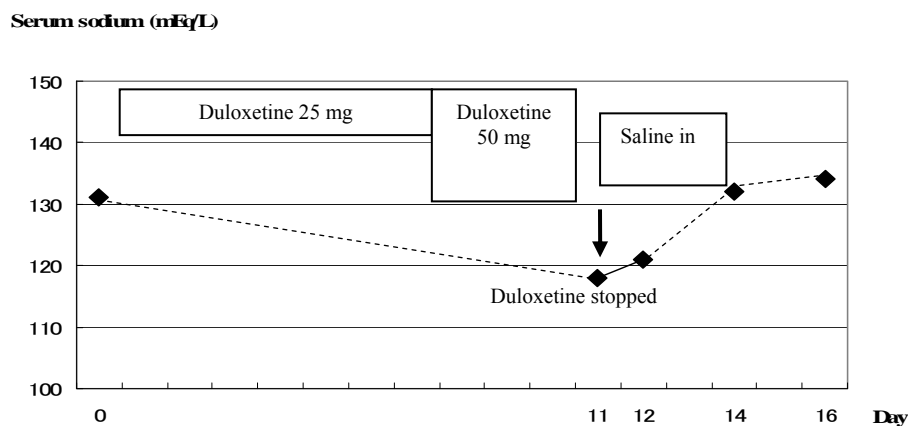


Figure 1.

Figure 1 shows the course of treatment and the changes in the serum sodium concentration of the case subject.

Severe hyponatremia occurred 10 days after the initiation of duloxetine therapy, and resolved 5 days after the discontinuation of duloxetine therapy with 3 days salt replacement therapy.

DISCUSSION

Symptoms of SIADH characterized by hyponatremia are nonspecific and range from mild lethargy, insomnia, headache and confusion to coma [4]. Awareness of this pathological condition is important because serious hyponatremia may be mistaken for worsening of depression, as features of hyponatremia

mimic certain depressive symptoms. Even more important is awareness that most episodes of serious drug-induced hyponatremia are reversed rapidly through discontinuation of treatment with the suspected drug, initiation of fluid restriction, and/or salt intake [4].

A number of physiologic changes in water homeostasis may predispose the elderly to hypona-

tremia of any etiology. In the elderly, the maximal diluting and concentrating capacity of the kidney is impaired [5] and ADH secretion may be slightly increased [6]. The ADH response to osmolar stimuli has been shown to be greater in the elderly than in young control subjects [7]. This increased osmosensitivity may increase the risk of SIADH. The risk of developing SIADH seems to increase with female sex, previous history of hyponatremia, medical comorbidities, and concomitant drugs known to cause hyponatremia or alter secretion of ADH [8]. Therefore, the diagnosis of SIADH is one of exclusion, when no physiological cause of hyponatremia can be identified or inferred.

The pathologic findings obtained for our case subject can be summarized as follows: 1) low baseline serum sodium level before the start of duloxetine therapy; 2) emergence of hyponatremia associated with neurological symptoms after 9 days of duloxetine treatment (during which time the dose was increased); 3) serum sodium and physical symptoms returned to normal shortly after discontinuation of duloxetine therapy; and 4) replacement of saline intake to maintain serum sodium levels was not needed subsequently.

There seems to have been some sort of morbidity present in combination with SNRI-induced SIADH. This patient had all the features of SIADH according to the criteria [9], and may also have been suffering from a salt deficiency during treatment with duloxetine because the patient's urine osmolality was not that high. However, the laboratory data showed that the patient's ADH level was not suppressed appropriately despite low plasma osmolality, and the clinical course showed that the serum sodium level decreased excessively when an SNRI was used for a short period, and normalized when use of the SNRI was discontinued. Therefore, SNRI-induced SIADH and hyponatremia were suspected in our case subject. To our knowledge, there are few case reports on duloxetine-related severe hyponatremia resulting in a diagnosis of SIADH that have been presented with multiple laboratory data, including ADH levels.

SSRI-induced hyponatremia is probably secondary to the development of SIADH [10]. The mechanism of SIADH with SSRIs/SNRIs remains unclear. One proposed hypothesis involves SIADH induction via the release of ADH (serotonin effects on 5-HT₂ and 5-HT_{1C} receptors) or increased renal responsiveness to ADH, which is supported by animal studies [11]. SSRIs/SNRIs inhibit norepinephrine reuptake to a certain extent, which suggests that norepinephrine

induction of ADH release via α_1 -adrenergic receptors may lead to SIADH induction [4]. Drug interactions between SSRIs/SNRIs and medications that can cause hyponatremia are another possible explanation. SSRIs are known to inhibit a number of cytochrome P450 isoenzymes [4]. This inhibition leads to elevated serum concentrations of these medications, which in turn augments their effects on sodium homeostasis.

SIADH has been reported to occur in between 0.5% to 32% of patients receiving SSRIs [3]. However, the frequency of SIADH in the elderly is extremely high, and ranges from 12% to 33% [10]. It is not easy to predict severe hyponatremia when initiating treatment with an SSRI or SNRI. Previous descriptive case studies have reported that the risk of duloxetine-related hyponatremia seems to be increased mainly in older female patients or during the week after treatment initiation [12]. In some case reports, however, it was reported in male non-elderly patients, or 3 months after duloxetine treatment initiation [13, 14]. One case report presented a dose-related effect, and another suggested a lower body weight in the development of hyponatremia with duloxetine [13, 15], although most of the published case reports did not indicate such a dose-dependent relationship. It has been reported that the incidence of SSRI-induced SIADH is fairly similar for different SSRIs [1]. There appears to be little evidence to suggest that switching patients experiencing SSRI- or SNRI-induced SIADH to a different SSRI or SNRI would result in a higher level safety.

Multiple factors, sometimes overlapping, may predispose the elderly to SSRI/SNRI-related hyponatremia. Moreover, the symptoms of hyponatremia can easily be misinterpreted as a worsening of depressive disorder. Therefore, when patients are placed on SSRIs or SNRIs, clinicians should give careful consideration to any medical comorbidities, conditions, or drug interactions, and monitor serum sodium concentrations during the entire course of treatment in order to be able to detect and treat hyponatremia and/or SIADH early on.

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