DULOXETINE- ASSOCIATED HYPONATREMIA: A CASE OF DRUG INDUCED SIADH

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Abstract

Hyponatremia is a common electrolyte disturbance that may result from various etiologies, including adverse drug reactions. Syndrome of inappropriate antidiuretic hormone secretion (SIADH) is a well-recognized cause, particularly associated with certain antidepressants. We report a case of a 54-year-old female who presented with dizziness, headache, fatigue, nausea, and vomiting following the addition of duloxetine and pregabalin for chronic musculoskeletal pain. Laboratory findings revealed severe hyponatremia (serum sodium 116 mEq/L) with low serum osmolality (225 m Osm/kg), suggestive of SIADH. The suspected offending drug was discontinued, and the patient was managed with hypertonic saline, antiemetics, and later oral tolvaptan. Gradual improvement in serum sodium levels to 132 mEq/L was observed, with resolution of symptoms. This case highlights the importance of early recognition of drug-induced hyponatremia and prompt management to prevent complications.

KEYWORDS: Duloxetine, SIADH, Hyponatremia

INTRODUCTION

Hyponatremia, defined as a serum sodium concentration of less than 135 mEq/L, is one of the most commonly encountered electrolyte abnormalities in clinical practice. It may present with a wide spectrum of clinical manifestations, ranging from mild, non-specific symptoms such as nausea, headache, and fatigue to severe neurological complications including confusion, seizures, and coma [1]. Among the various etiologies, the syndrome of inappropriate antidiuretic hormone secretion (SIADH) is a major cause of euvolemic hyponatremia and is frequently associated with the use of certain medications [2].

SIADH is characterized by excessive release of antidiuretic hormone (ADH) or increased renal responsiveness to it, resulting in impaired water excretion, dilutional hyponatremia, and decreased serum osmolality [3,4]. Drug-induced SIADH is increasingly recognized in clinical settings, particularly with the widespread use of psychotropic and centrally acting medications [5]. Antidepressants, especially selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs), are among the most commonly implicated drug classes [6,7].

Duloxetine, a widely prescribed SNRI, is commonly used in the management of major depressive disorder, generalized anxiety disorder, diabetic neuropathy, fibromyalgia, and chronic musculoskeletal pain [8]. It exerts its therapeutic effects by inhibiting the reuptake of serotonin and norepinephrine in the central nervous system, thereby enhancing their synaptic availability [9]. However, this increase in serotonergic activity is believed to play a key role in the development of SIADH. Serotonin can stimulate the release of antidiuretic

hormone from the hypothalamus, leading to inappropriate water retention. Additionally, duloxetine may increase renal sensitivity to ADH, further contributing to impaired free water clearance and dilutional hyponatremia [10,11].

The risk of duloxetine-induced SIADH is higher in certain populations, particularly elderly individuals, females, and patients receiving concomitant medications that affect central nervous system function or fluid balance [12]. The onset of hyponatremia is often acute, typically occurring within the first few days to weeks after initiation of therapy, making early monitoring essential.

Apart from hyponatremia, duloxetine is associated with a range of other adverse drug reactions. Common side effects include nausea, dry mouth, dizziness, somnolence, constipation, and fatigue [13]. It may also cause increased blood pressure, hepatotoxicity, and, in some cases, serotonin syndrome, especially when combined with other serotonergic agents [14]. Withdrawal symptoms such as irritability, insomnia, and headache may occur upon abrupt discontinuation. Although generally well tolerated, these adverse effects necessitate careful patient selection and monitoring.

Early recognition of drug-induced SIADH, particularly in patients receiving duloxetine, is crucial to prevent serious complications. Prompt identification, discontinuation of the offending agent, and appropriate management can significantly improve patient outcomes [15,16]. This case report aims to highlight duloxetine as a potential cause of SIADH and emphasizes the importance of clinical vigilance in patients presenting with unexplained hyponatremia [17].

CASE REPORT

A 54-year-old female patient presented with complaints of dizziness, headache, fatigue, nausea, and vomiting for a duration of three days. She had a history of chronic musculoskeletal pain, for which she was initially treated with tablet piroxicam, amitriptyline, methylprednisolone, and gabapentin for two weeks. Due to inadequate pain relief, pregabalin and duloxetine were added to her treatment regimen.

The patient developed the above symptoms within three days of initiating the additional medications. On clinical examination, she was conscious and oriented but appeared fatigued. Her vital signs were stable. There were no signs of dehydration or edema.

Laboratory investigations revealed a significantly reduced serum sodium level of116mEq/L, indicating severe hyponatremia. Serum osmolality was found to be 225 mOsm/kg, consistent with hypotonic hyponatremia. Other laboratory parameters were within normal limits. Based on clinical and laboratory findings, a diagnosis of drug-induced SIADH was considered and on the Naranjo adverse drug reaction probability scale, a score of 7 was obtained, indicating a probable relationship between duloxetine and the development of SIADH in this patient.

The suspected offending medication, particularly duloxetine, was discontinued immediately. The patient was managed with 3% hypertonic saline under careful monitoring. Symptomatic treatment included INJ. PROCHLORPERAZINE and INJ. ONDANSETRON for nausea and vomiting, along with INJ. PANTOPRAZOLE for gastric protection.

As the patient's sodium levels began to improve, she was transitioned to oral TABLET TOLVAPTAN, a vasopressin receptor antagonist, to promote free water excretion. Over the course of treatment, her serum sodium levels gradually increased to 132 mEq/L, accompanied by significant symptomatic improvement.

The patient remained hemodynamically stable and was discharged with advice for follow-up and avoidance of the suspected offending drug.

DISCUSSION

Hyponatremia is a commonly encountered electrolyte abnormality, with the syndrome of inappropriate antidiuretic hormone secretion (SIADH) being a major underlying cause, particularly in drug-induced cases. Several studies have established a strong association between antidepressant use and SIADH. The review by

Ellison and Berl[1] described SIADH as a key mechanism of euvolemic hyponatremia, emphasizing its frequent link with medications.

In the present case, duloxetine was considered the most likely causative agent for the development of hyponatremia. This assumption is supported by the clear temporal relationship, as the patient developed symptoms within three days of initiating the drug. In addition, a marked improvement in both clinical symptoms and serum sodium levels was observed following discontinuation of duloxetine, indicating a positive dechallenge response. Other possible causes of hyponatremia, including renal impairment, endocrine abnormalities, and fluid imbalance, were carefully evaluated and ruled out, further strengthening the likelihood of drug-induced SIADH. Similar findings have been reported in previous studies by Sato et al. (2022) and Yoshida et al. (2019), where duloxetine was identified as a triggering factor. From a pharmacological perspective, duloxetine enhances serotonergic activity, which can stimulate the release of antidiuretic hormone and increase renal sensitivity to it, ultimately leading to water retention and dilutional hyponatremia. Based on established causality assessment criteria, this adverse drug reaction can be classified as probable.

The onset of severe hyponatremia closely followed the initiation of duloxetine therapy. A comprehensive review by *De Picker et al*[3] highlighted that antidepressants, particularly SSRIs and SNRIs, significantly increase the risk of hyponatremia, with a higher incidence observed in elderly females. This finding is consistent with the demographic and clinical profile of the current patient.

Similarly, *Liamis et al*[2] reported that drug-induced hyponatremia often develops within the first few days to weeks of therapy, which aligns with this case where symptoms appeared within three days of adding duloxetine. A case-control study by *Movig et al*[9] further supported the association between antidepressant use and hyponatremia, demonstrating an increased risk particularly during the early phase of treatment.

The mechanism of duloxetine-induced SIADH has been discussed in studies such as *Jacob and Spinler*[4] where antidepressants were shown to enhance antidiuretic hormone secretion or increase renal sensitivity to ADH, leading to water retention and dilutional hyponatremia. In addition, *Kirby and Ames* [7] emphasized that elderly patients are particularly vulnerable due to altered renal function and increased sensitivity to ADH.

In comparison with existing literature, the severity of hyponatremia observed in this patient (serum sodium 116 mEq/L) is notable. While many reported cases describe mild to moderate hyponatremia, studies such as *Fabian et al*[8] have documented severe symptomatic cases requiring urgent intervention. The presenting symptoms in this case, including dizziness, nausea, and fatigue, are consistent with those described in these studies.

Management of this case was in line with established recommendations. The expert panel guidelines by *Verbalis et al*[12] emphasize immediate discontinuation of the offending drug and cautious correction of sodium levels. The use of hypertonic saline in severe symptomatic hyponatremia is strongly supported by these guidelines.

Furthermore, the use of tolvaptan in this patient reflects findings from studies such as *Sherlock and Thompson* [11] which describe vasopressin receptor antagonists as effective agents in the management of SIADH by promoting free water excretion. Compared to traditional methods like fluid restriction, tolvaptan offers a more targeted and efficient approach.

Unlike some reports in the literature where hyponatremia may recur or persist, the patient in this case showed a favorable outcome with normalization of sodium levels following appropriate intervention. This outcome is comparable to cases discussed by *Spigset* [5] where withdrawal of the causative drug led to complete recovery.

Overall, this case aligns well with existing literature in terms of risk factors, pathophysiology, and management. It also reinforces observations from multiple studies that duloxetine can precipitate rapid-onset SIADH, particularly in high-risk individuals, highlighting the importance of early recognition and intervention.

CLINICAL SIGNIFICANCE

This case underscores the clinical importance of recognizing drug-induced SIADH as a reversible cause of severe hyponatremia. Early identification, discontinuation of the offending agent, and appropriate management can lead to rapid recovery and prevent life-threatening complications. It also highlights the need for cautious use of antidepressants such as duloxetine, particularly in high-risk populations.

CONCLUSION

Drug-induced hyponatremia remains an important yet often under-recognized clinical entity, particularly in patients receiving centrally acting medications such as antidepressants. This case highlights duloxetine-induced SIADH as a significant and potentially life-threatening cause of severe hyponatremia, especially in middle-aged and elderly female patients.

The rapid onset of symptoms following drug initiation, along with laboratory findings of hypotonic hyponatremia, emphasizes the need for high clinical suspicion and early diagnosis. Timely identification and prompt discontinuation of the offending agent played a crucial role in the favourable outcome observed in this patient.

The case also reinforces the importance of appropriate and cautious management strategies, including the use of hypertonic saline in severe symptomatic cases and vasopressin receptor antagonists such as tolvaptan for controlled correction of sodium levels. Avoiding rapid overcorrection is essential to prevent serious neurological complications such as osmotic demyelination syndrome.

Furthermore, this report underlines the significance of rational prescribing and close monitoring, particularly when initiating antidepressants in high-risk populations or in patients receiving multiple CNS-active medications. Regular monitoring of serum electrolytes during the early phase of therapy can aid in early detection and prevention of adverse outcomes.

In conclusion, this case contributes to the growing body of evidence linking duloxetine with SIADH and highlights the importance of clinical vigilance, individualized patient care, and multidisciplinary management in ensuring optimal patient outcomes. Increased awareness among healthcare professionals can facilitate early intervention and reduce morbidity associated with drug-induced electrolyte disturbances.

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