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Divalproex Sodium-Induced Hyponatremia: A Case Report with Positive Rechallenge

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Case Report

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ABSTRACT

This report describes the case of a 56-year-old African American male who experienced severe hyponatremia after receiving Divalproex sodium therapy for bipolar I disorder on various occasions. Divalproex re-initiation caused a recurrence of hyponatremia, leading to discontinuation of the drug and initiation of Lithium. Although most cases of hyponatremia are asymptomatic, a sudden drop in sodium levels can be fatal. Therefore, it is important to be aware of the risk of hyponatremia in individuals undergoing bipolar I disorder therapy with Divalproex. This case highlights the need to monitor sodium levels in patients taking valproic acid.

Keywords: Valproic acid; hyponatremia; side effects; low sodium; bipolar I disorder.

1. INTRODUCTION

Divalproex sodium is an anticonvulsant and mood-stabilizing drug used primarily to treat epilepsy and bipolar I disorder [1]. It was approved in 1978 in the United States by the Food and Drug Administration (FDA) as an antiepileptic drug for the treatment of absence seizures [2] and bipolar disorders in 1995 [3]. Some side effects associated with Divalproex include teratogenicity, elevated hepatic enzyme levels, hepatotoxicity, weight gain, and alopecia [4]. Given that Divalproex sodium is administered as a sodium salt, it can cause hypernatremia at high doses [5]. This case report describes a patient with bipolar I disorder who developed hyponatremia during long-term treatment with Divalproex sodium.

2. CASE PRESENTATION

A 56-year-old African American male was seen in a clinic for a follow-up visit for his bipolar I disorder, which was diagnosed 25 years ago. He also complained of fatigue, dizziness, nausea, headaches, muscle weakness, and muscle cramps. He denied excessive thirst, excessive urination, dry mouth, or excessive water consumption. He was currently taking Divalproex sodium for 1000mg twice daily for his bipolar I disorder. He was unemployed, single, had no children, and was homeless.

His past medical history was significant for obesity and hyperlipidemia, which was treated with Atorvastatin. He also had a past history of hospitalization following three suicide attempts. Additionally, he has a history of psychotic symptoms characterized by persecutory delusion, which was previously treated with olanzapine, which was discontinued following the patient's request after the symptoms subsided. His family history was positive for bipolar I disorder in his mother, who responded well to Divalproex sodium.

On examination, he talked excessively and was socially disinhibited. He had an irritable mood and affect and a linear thought process. There was adequate attention and concentration and no suicidal ideation. He was oriented to time, place, and person with fair insight and judgment.

A Comprehensive Metabolic Panel showed a serum sodium level of 125mEq/L (reference range 136-145mEq/L). Other renal parameters, thyroid-stimulating hormone levels, Complete Blood Count, Serum Vitamin B12 level, and liver function tests were within normal limits. However, the osmolality of the serum and urine was not conducted as these tests were not routinely available in the facility where the patient was seen. Divalproex sodium level was less than or equal to 100mcg/ml on all occasions except once when it was 109mcg/ml.

Following the review of the patient's symptoms, medications, and laboratory investigation results, he was treated by the medical team with water restriction and oral sodium tablets. His symptoms improved, and his serum sodium level returned to normal at 139mEq/L (referenc range 136-145mEq/L). He continued taking his Divalproex sodium, and on his one-week follow-up visit, his serum sodium level had decreased again to 133mEq/L (reference range 136-145mEq/L). As a result, the Divalproex sodium dosage was reduced to 750mg twice daily and further decreased to 500 mg twice daily after linking the patient's hyponatremia with Divalproex sodium as the likely cause. When this dose reduction did not improve the serum sodium level, and the patient's symptoms returned, Divalproex sodium was changed to Lithium 600 mg twice daily, which controlled the bipolar I disorder symptoms.

3. DISCUSSION

In this case, Divalproex sodium-induced hyponatremia occurred in a bipolar I disorder

patient receiving treatment with Divalproex sodium. Valproate has been reported to cause a syndrome of inappropriate antidiuretic hormone secretion (SIADH) syndrome-like hyponatremia among patients using the drug to treat epilepsy [6]. Very few cases of valproate-induced hyponatremia in patients using the medication to treat psychiatric illnesses have been reported [6].

Some of the possible mechanisms suggested for this hyponatremia include an increase in antidiuretic hormone (ADH) secretion, an increase in renal sensitivity to ADH, a decrease in hypothalamic sensitivity, and inhibition of vasopressin removal [6,7,8]. While the likely mechanism of hyponatremia development in this patient may be challenging to ascertain, resolution of hyponatremic symptoms, improvement in serum sodium after discontinuation of Divalproex sodium, and drop in serum sodium level when Valproate was re-initiated (rechallenge) indicated that Divalproex sodium was responsible for the patient's hyponatremia.

Factors that could have contributed to the development of hyponatremia in this patient include the previous use of antipsychotics and the early onset of psychiatric illness [9,5,10]. However, at the time of presentation, the patient was taking any antipsychotics, making Divalproex sodium the most likely cause of his hyponatremia.

In this case report, the patient holds significant importance for several reasons. First, Divalproex sodium-induced hyponatremia is rare. While other medications like antidepressants, antipsychotics, and anticonvulsants like carbamazepine are established causes of hyponatremia [10], few case reports have described Divalproex sodium as a cause of hyponatremia [11], [6], [9], [5]. Second, very few cases have reported hyponatremia in patients using Divalproex sodium for the treatment of neuropsychiatric illnesses like bipolar I disorder despite being a common FDA-approved medication for the disorder [9], [12], [13]. Also, given that the underlying cause of hyponatremia due to antiepileptic drugs is not scientifically validated, it remains unclear what contribution the primary central nervous system dysfunction leading to epilepsy might have on the cause of inappropriate ADH production [14]. Also, given that antipsychotics have been shown to increase the risk of hyponatremia in patients using antiepileptic drugs [15], it is essential to have an exhaustive discussion on the issue of Divalproex sodium-induced hyponatremia in patients using the medication for the treatment of psychiatric conditions as they are likely to be using antipsychotic medication at some points in their treatment.

Most of the cases of hyponatremia due to anticonvulsants in the literature were not accompanied by rechallenge tests [13], [9], [5]. In this case report, Divalproex sodium re-initiation was associated with the re-emergence of hyponatremia in the patient, demonstrating that Divalproex sodium was the most likely cause of the observed hyponatremia. Hyponatremia is also commonly missed as a side effect of antiepileptic drugs for many reasons. Many patients with hyponatremia secondary to antiepileptic medications do not manifest symptoms. Most patients (close to 70%) in a study by Yamamoto et al. with serum sodium less than 130mEq/L were asymptomatic [15]. Yet, an abrupt drop in serum sodium could be life-threatening. Therefore, it is important to be aware of the risk of hyponatremia in patients taking Divalproex sodium to treat bipolar I disorder.

4. CONCLUSION

Recurrent hyponatremia was observed in a patient following the use of Divalproex sodium to treat bipolar I disorder. Important aspects of the case presentation are the rarity of Divalproex sodium-induced hyponatremia compared to other anticonvulsants, the paucity of case reports describing Divalproex sodium-induced hyponatremia among patients with psychiatric illnesses, the absence of clinical symptoms in some patients experiencing Divalproex sodium-induced hyponatremia and the fatalities associated with hyponatremia if it is unnoticed or untreated. All these points demonstrate the importance of determining the baseline serum sodium levels and monitoring serumsodium periodically in patients taking Divalproex sodium for neuropsychiatric illnesses.

CONSENT AND ETHICAL APPROVAL

As per international standard or university standard guideline patient consent and ethical approval has been collected and preserved by the authors.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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