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Acute hyponatremia with accompanying hyperammonemia secondary to divalproex sodium: A case report

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Abstract

Divalproex sodium (DVP) is an antiepileptic medication that also has mood stabilizing properties for patients with mental health disorders. Currently, there are a small number of case reports discussing the incidence of hyponatremia that occurs as an adverse effect of DVP. After completion of a thorough literature search, we present the first case report describing acute hyponatremia with accompanying hyperammonemia secondary to DVP use. This case describes a 44-year-old male patient who experienced hyponatremia with accompanying hyperammonemia following initiation of DVP for schizoaffective disorder. This case highlights the need for clinicians to consider monitoring electrolytes, in addition to liver function and platelets, with the initiation of therapy or increase in daily dosage. Given the drug's action at voltage-gated sodium channels, changes in serum sodium could be expected.

Keywords: divalproex sodium, valproate, valproic acid, hyponatremia, hyperammonemia

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Background

Divalproex sodium (DVP) is a first generation antiepileptic medication, approved by the Food and Drug Administration, for use in patients with epilepsy, mania in bipolar disorder, and migraine prophylaxis.[1] First generation antiepileptic medications are well known for their fast inactivation of the voltage-gated sodium channel after depolarization; specifically, DVP is thought to increase the availability of the inhibitory neurotransmitter gamma-aminobutyric acid in the synaptic cleft, thus increasing its activity and actions at the post-synaptic calcium channel receptor.[2] Hyperammonemia is a rare but established adverse effect associated with DVP use. Hyponatremia is not usually correlated with DVP use; its prevalence is more established with second generation antiepileptic medications, such as carbamazepine and oxcarbazepine.[1,3,4] In this case report, a male patient who experienced acute hyponatremia with accompanying hyperammonemia secondary to DVP use is discussed. A literature review is also provided.

Patient Case

A 44-year-old white male presented to the emergency department with complaints of chest pain. His past medical history was significant for hypertension, hyperlipidemia, diabetes, coronary artery disease, myocardial infarction, and schizoaffective disorder. It was unknown if he was prescribed medications for his physical health conditions. Upon further interview, the patient admitted to "hearing voices and seeing things," as well as 2 weeks of medication noncompliance with oral haloperidol. The patient also reported last receiving haloperidol decanoate intramuscular injection 2 months prior to admission. The patient's past psychiatric history was also significant for multiple inpatient admissions and a past suicide attempt. During the patient's 24-hour stay in the emergency department, the patient received aspirin 162 mg. Labo-

ratory findings showed negative troponin and creatine kinase-muscle/brain levels when trended twice over 4 hours, and an electrocardiogram in normal sinus rhythm to help rule out a cardiac abnormality.

Psychiatry evaluated the patient's mental status while in the emergency department. Although cooperative, oriented to person, place, and time, and with a concrete thought process, the patient was noted to have a labile affect with fair insight and impaired judgment with regard to his mental illness. The patient endorsed passive suicidal ideation with both auditory and visual hallucinations of "his dead father and voices telling him to hurt himself." Once the patient was medically cleared, he was admitted to the psychiatry unit. On hospital day (HD) 2, oral haloperidol was restarted at the outpatient dose of 10 mg twice daily, benztropine 1 mg twice daily for extrapyramidal symptoms, and clonazepam 0.5 mg 3 times daily for anxiety. The patient also received haloperidol decanoate 200 mg intramuscular on HD 3. There were no noted changes in auditory and visual hallucinations on HD 7, so the patient's evening dose of haloperidol was increased to 15 mg. Furthermore, the patient was initiated on DVP 1000 mg at bedtime to help with irritability and intrusiveness on HD 8.

On HD 13, the patient became more disorganized in his thought process and had an episode of urinary incontinence, as per overnight nursing notes. The patient was not oriented to place or time; he was able to identify that he was in a hospital but thought that it was a different one. Prior to the onset of these changes in mental status, there had been no improvement in the patient's auditory and visual hallucinations noted from admission. Laboratory studies were performed to determine an etiology for the acute change in the patient's mental status. Laboratory values revealed hyperammonemia (105 μg/dL; control <56 μg/dL), hyponatremia (122 mEq/L; control 133 to 145 mEq/L), and hypochloremia (89 mEq/L; control 96 to 108 mEq/L) on HD 13, down from a sodium of 133 mEq/L and chloride of 100 mEq/L on HD 1 (Figure). Therapeutic drug monitoring of valproic acid serum level was subtherapeutic at 29.1 mg/dL on HD 13 as well despite DVP being started on HD 8. Once transferred to the general medicine floor, the patient's initial treatment for hyperammonemia involved discontinuing DVP and initiating lactulose. Haloperidol, benztropine, and clonazepam were also discontinued due to the presence of hyponatremia. A free water restriction was put into place, and a total of 2 L of 0.9% NaCl was given via intravenous infusion over 22 hours to medically treat these electrolyte imbalances. The patient remained on the general medicine floor for 48 hours to assess his mental status, electrolyte, and ammonia levels. Upon initiation of these treatments and subsequent monitoring, the ammonia levels began to trend downwards and the sodium and chloride levels trended upwards. The acute mental status changes had completely resolved as well; the patient was able to orient himself and communicate to the consulting nephrologist that he had experienced polydipsia after the DVP had been initiated. The patient was readmitted to the psychiatry unit with serum sodium of 130 mEq/L and serum chloride of 95 mEq/L. Serum ammonia was not rechecked at this time. The patient continued to receive lactulose to further decrease his ammonia level.

Haloperidol 5 mg twice daily and olanzapine 5 mg at bedtime were initiated for continued psychosis on HD 15. On HD 16, the patient denied having both visual and auditory hallucinations for the first time during his inpatient visit. Additionally, his free water restriction was discontinued on HD 16 based on stabilization of the serum sodium level. At discharge on HD 18, serum sodium and chloride were at baseline (133 mEq/L and 100 mEq/L, respectively), and the serum ammonia at 63 μg/dL. The patient was discharged on olanzapine 5 mg at bedtime, and haloperidol 10 mg in the morning and 15 mg at bedtime, and to receive haloperidol decanoate 200 mg intramuscular injection in 3 weeks.

Discussion and Literature Review

Based upon the patient's clinical presentation, the diagnostic criteria for hyponatremia with accompanying hyperammonemia was met.[5,6] It was observed by staff that the patient had experienced a change in mental status, as evidenced by an increase in disorganized thinking and an episode of urinary incontinence. The etiology of his altered mental state was confirmed by laboratory values, which indicated an elevated serum ammonia level. Laboratory values were also able to confirm an additional diagnosis of hyponatremia, based on decreased serum sodium and chloride levels from admission. Both abnormalities were resolved with recommended treatments[7,8]; the patient's mental status returned to baseline as well. According to the Naranjo adverse drug reaction probability scale,[9] valproate acid use was the probable cause of hyponatremia and hyperammonemia in this patient. These reactions occurred after starting DVP, resolved upon discontinuation of DVP, and no other causes were identified within the relevant time frame of the reactions. Hyponatremia is sometimes associated with antipsychotics including haloperidol,[10] however due to the consistent use of haloperidol before, during, and after the episode of hyponatremia this patient experienced, this potential cause was ruled out.

A literature search was conducted on November 24, 2017 using PubMed to identify articles published in English with the following key terms: *hyponatremia*, *hyperammonemia*,

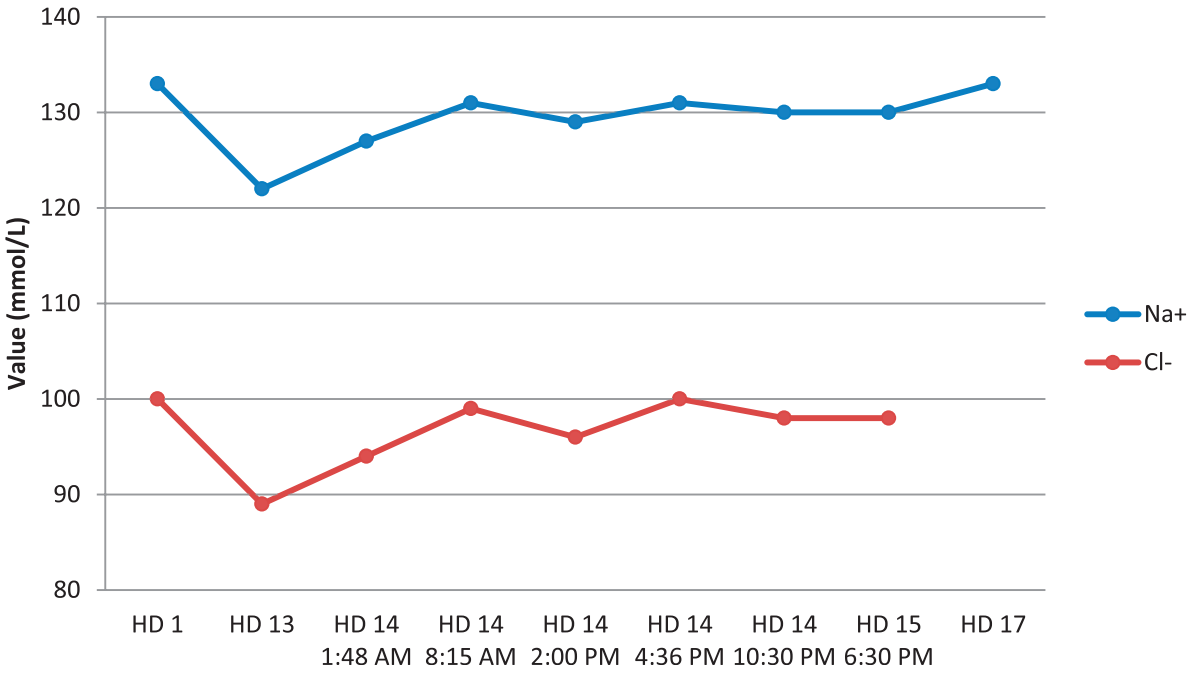

FIGURE: Patient laboratory value trends: Na+ and Cl– (HD = hospital day)

and *valproic acid*. This search yielded 2 results, neither of which were relevant to this patient's case. An additional literature search conducted using PsycINFO with the same key terms yielded no results. Thus, to the best of our knowledge, there are no published reports of hyponatremia with accompanying hyperammonemia from valproate use. When the term *hyperammonemia* was removed, 41 results from both databases were reviewed for articles discussing hyponatremia without accompanying hyperammonemia. To the best of our knowledge the occurrence of hyponatremia with accompanying hyperammonemia from valproate use has not been documented in the literature. Within this text is summarized the relevant literature related to hyponatremia with accompanying hyperammonemia in the setting of valproate use.

Druschky et al[4] retrospectively analyzed utilization patterns and risk factors from antiepileptic drug use using data in 82 387 patients from Arzneimittelsicherheit in der Psychiatrie, a German drug safety program, between 1993 to 2013. The number of patients diagnosed with schizoaffective disorder was not reported; however, the study reported that valproate was used in 50% of patients who had manic episodes from 2005 to 2009, making it one of the more frequently used treatment modalities. In total, 87 cases of hyponatremia were identified from 630 adverse drug reactions. Six of these cases were patients who were using divalproex, or 6.9% of all hyponatremia cases. Each of the 6 patients who experienced severe hyponatremia were those using both DVP and another antiepileptic agent. Gandhi et al[11] also performed a retrospective analysis. This cohort study examined the 30-day risk of hospitalization for hyponatremia from a new antiepileptic prescription versus medication nonusers in older adults using data from administrative healthcare databases in Ontario, Canada between 2003 to 2015. Patients were grouped based on the antiepileptic prescription(s) received. The cohort of patients who used valproate, phenytoin, or topiramate versus medication nonuse was associated with 0.17% 30-day hospitalization risk for hyponatremia versus 0.06%, respectively; however, the risk associated with carbamazepine use was 0.39% versus medication nonuse at 0.05%. Additionally, it was determined that patients receiving phenytoin had a 2.6 times greater risk when compared to valproate.

Three case reports discussed valproate use resulting in hyponatremia. Branten et al[7] described a 53-year-old male patient with asymptomatic hyponatremia from valproate. The patient had been prescribed valproate for management of generalized idiopathic epilepsy for almost 20 years; he was currently taking 2000 mg daily. His serum sodium level was noted to be 128 mEq/L during a regular outpatient visit. A diagnosis was made based on valproate being his only medication, previously recorded serum sodium levels within normal range and low plasma osmolality of 260 mOsm/kg. The patient resumed valproate after a fluid restriction corrected the electrolyte abnormality, but at 1500 mg daily. Gupta et al[8] discussed a 54-year-old female patient presenting with somnolence after an intentional ingestion of 7500 mg of valproate. Although the rest of her physical examination was unremarkable, her serum sodium level was recorded at 99 mEq/L in the emergency department. The patient was

admitted to the medical intensive care unit, where other laboratory findings of low plasma osmolality (211 mOsm/kg) and high urine osmolality (115 mOsm/kg) supported a diagnosis of hyponatremia. Her serum sodium rose and mental status returned to baseline upon discontinuation of valproate. Beers et al[12] reviews 4 case reports of symptomatic hyponatremia from the Netherlands in patients using valproate. Patient A was a 67-year-old female patient who was prescribed 500 mg twice daily of valproate for epilepsy. She presented to the hospital due to her inability to walk without assistance, and it was discovered that her serum sodium level was 120 mEq/L. The patient was restarted on valproate after her serum sodium levels stabilized but was switched to gabapentin when hyponatremia returned. Patient B was a 71-year-old female patient who was prescribed 300 mg 3 times daily of valproate and 50 mg daily of phenobarbital for epilepsy control. She had a history of hyponatremia, but from diuretic medication use. Her serum sodium level at presentation to the hospital was 125 mEql/L. Similarly to Patient A, she was switched to topiramate because hyponatremia returned once serum sodium levels had stabilized and valproate was resumed. Patient C was an 88-year-old female patient who was prescribed 300 mg daily of valproate and 50 mg daily of phenobarbital for epilepsy control. She presented to the hospital with sudden malaise, somnolence, nausea and vomiting, and 4 kg weight loss in 10 days. Her serum sodium level was 116 mEq/L and normalized once valproate was discontinued. Patient D was a 57-year-old female patient who was prescribed 1000 mg twice daily of valproate and 200 mg daily of lamotrigine for epilepsy. Similarly to Patient C, she presented to the hospital with symptoms of confusion, memory impairment, somnolence, and severe hyponatremia. Her serum sodium level was 116 mEq/L. Valproate was still administered to the patient but at a decreased dose of 1500 mg daily. Additionally, the patient's lamotrigine dose remained constant. With a fluid restriction, her serum sodium level rose and normalized.

Conclusion

We present here a probable case of acute hyponatremia with accompanying hyperammonemia secondary to DVP. Although clinicians are more inclined to monitor a patient's liver function and complete blood count due to the known risks of hepatotoxicity, hyperammonemia, and thrombocytopenia, this case shows the importance of monitoring electrolytes, especially after an initiation of therapy or an increase in daily dosage. As there are no established guidelines for the monitoring of electrolytes upon initiation of DVP, we would suggest that monitoring electrolytes occur with the same frequency as liver function and platelets. Based on the drug's activity at the voltage-gated sodium channels, it could be argued that effects on serum sodium may be expected in patients.

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