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CARBAMAZEPINE-INDUCED HYPONATREMIA

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ABSTRACT
Carbamazepine is a widely used antiepileptic and mood-stabilizing medication, is known to cause clinically significant adverse effects such as hyponatremia, which may often go unnoticed in clinical practice. A 30-year-old male with a history of seizure disorder on maintenance therapy with Carbamazepine (1-0-2), chronic alcohol consumption, and nicotine dependence presented to the emergency department with involuntary movements of all limbs, headache, giddiness, fever, and a single seizure episode. On admission, his heart rate was 135 bpm, and serum sodium measured 118 mmol/L, confirming hyponatremia, while brain MRI revealed no acute intracranial pathology. A diagnosis of Carbamazepine-induced hyponatremia was established. The patient was promptly managed with intravenous Paracetamol, Thiamine, Levetiracetam, Ceftriaxone, and Tolvaptan, along with supportive therapy. Serum sodium levels normalized by the third day (138 mmol/L), and maintenance therapy included antiepileptic medication, gastric protection, and vitamin supplementation. He was discharged in stable condition with Quetiapine and vitamin therapy. This case highlights the importance of routine electrolyte monitoring in patients receiving prolonged Carbamazepine therapy, particularly those with chronic alcohol use, to prevent potential neurological complications associated with hyponatremia.

KEYWORDS: Epilepsy, seizure, Carbamazepine induced hyponatremia, SIADH, Electrolyte disturbance and Tolvaptan.

INTRODUCTION
Epilepsy is the fourth most common neurological disorder globally, affecting approximately 50 million individuals. The annual incidence is estimated at around 80 cases per 100,000 population. This chronic neurological condition imposes a significant burden on patients, families, and healthcare systems, with nearly 90% of the 70 million global cases reported from developing countries. Epilepsy comprises a spectrum of disorders characterized by recurrent, unprovoked seizures resulting from abnormal neuronal discharges in the brain.[1] Carbamazepine remains a cornerstone therapy in the management of various forms of epilepsy and neuropathic pain. Beyond its antiepileptic properties, it is also widely prescribed for the treatment of certain mood disorders, including bipolar disorder and acute mania. However, despite its therapeutic benefits, carbamazepine is associated with clinically relevant drug interactions, primarily due to its ability to inhibit or induce cytochrome P450 enzymes—most notably CYP3A4.[2]

One of the noteworthy adverse effects of carbamazepine therapy is hyponatremia, defined as a serum sodium (Na^+) concentration below 136 mmol/L, and considered clinically significant when levels fall between 135 and 145 mmol/L. Acute hyponatremia, developing within 48 hours, may result in serious neurological complications such as seizures, confusion, and coma, necessitating urgent medical attention to prevent morbidity and mortality.[3,4] Symptomatic manifestations typically occur when serum sodium levels drop to approximately 119 ± 9.1 mmol/L.[5] Asymptomatic hyponatremia is relatively common among patients receiving

carbamazepine, with subtle symptoms like dizziness and somnolence often overlooked in clinical practice.[6] The underlying mechanism involves increased secretion of antidiuretic hormone (ADH), heightened sensitivity of renal tubules to ADH activity, and upregulation of aquaporin-2 channel expression in renal cells. Additionally, potential pharmacodynamic interactions may exacerbate this adverse effect, resulting in a more pronounced decline in serum sodium levels.[7]

Here, this article we discussed a case of hyponatremia secondary to recent carbamazepine use. The patient exhibited a serum sodium concentration of 118 mmol/L and presented with complaints of headache, giddiness, fever, and a single episode of seizure.

CASE STUDY

A 30-year-old male was admitted to the emergency department with complaints of involuntary movements of both upper and lower limbs for 25 days, headache, giddiness, fever and a single episode of seizure. The patient is a chronic alcoholic for the past 40 years and has a history of nicotine dependence. There was no history of tongue bite, loss of consciousness, vomiting, or bowel and bladder incontinence.

He has a known history of seizure disorder for the past 3 years and has been on Carbamazepine (T. Carbamazepine 1-0-2) as maintenance therapy. MRI Brain revealed no acute intracranial abnormality. On admission, heart rate was 135 bpm (tachycardia) and serum sodium was 118 mmol/L, indicating hyponatremia.

ENT consultation noted difficulty in swallowing and throat pain; oropharyngeal mucositis was diagnosed and treated with multivitamins (1 amp in 100 ml NS) and Anabel gel (Choline salicylate + Lidocaine) TDS.

Psychiatric evaluation confirmed alcohol dependence syndrome, with relapse one month ago (average daily intake: 30 units/day; last intake: 7 days prior).

A diagnosis of Carbamazepine-induced hyponatremia was found.

Initial (stat) treatment included

- Inj. Paracetamol 1 g IV
- Inj. Thiamine 100 mg in 100 ml NS
- Inj. Levetiracetam 1.5 g in 100 ml NS
- Inj. Ceftriaxone 2 g
- T. Tolvaptan 15 mg
- Inj. Pantoprazole 40 mg

On days 2–3, sodium levels normalized (138 mmol/L) and therapy included

T. Paracetamol 650 mg (1-1-1), Inj. Thiamine 100 mg (1-0-1), T. Tolvaptan 15 mg, Inj. Ranitidine 40 mg (1-0-0) and T. Levetiracetam 500 mg (1-0-1).

On days 4–5, therapy was continued with

T. Paracetamol 650 mg (1-1-1), Inj. Thiamine 100 mg (1-0-1), T. Ranitidine 40 mg (1-0-0), T. Levetiracetam 500 mg (1-0-1), Syp. Oxetacaine + Aluminium hydroxide + Milk of Magnesia (1-1-1), T. Lorazepam 2 mg (1-1-1) and T. Alpha Lipoic Acid + Benfotiamine + Methylcobalamin + Pyridoxine (1-0-1).

Upon discharge, medications included

- T. Quetiapine 50 mg (SOS)
- Inj. Thiamine (100 mg) + Pyridoxine (100 mg) + Cyanocobalamin (1000 mcg) + Riboflavin (5 mg) + Nicotinamide (100 mg) + D-Panthenol (50 mg) in 100 ml NS (TDS).

LITERATURE REVIEW

Kaeley et al 2019 conducted a case study in 60-year-old woman presented with bilateral pedal edema for one month. Two months earlier, she experienced focal seizures with secondary generalization and was started on carbamazepine 200 mg thrice daily. She had a two-year history of hypertension managed with telmisartan 40 mg daily. Examination revealed euvolemia with pedal edema and stable vitals. Laboratory findings showed serum sodium 118 mEq/L, urine osmolality 317.3 mOsm/kg, and urinary sodium 49.7 mmol/L, with normal thyroid, adrenal, and renal function, confirming SIADH. Secondary causes such as malignancy, pulmonary disorders, hypothyroidism, and adrenal insufficiency were excluded. Carbamazepine-induced SIADH was suspected. The drug was discontinued, and levetiracetam 500 mg thrice daily, tolvaptan 30 mg once daily, and fluid restriction were initiated. Serum sodium improved gradually to 122 mEq/L on day 3, 125 mEq/L on day 4, and 135 mEq/L after one week, indicating successful correction of hyponatremia.[8]

Palacios Argueta et al. (2018) reported a case of a 44-year-old Guatemalan woman who presented with left knee pain, fatigue, and bilateral leg cramps. She had been self-medicating with carbamazepine (600 mg/day) and prednisone (20 mg/day) for the past week. Physical examination showed port-wine stains and mild calf hypertrophy, consistent with Klippel-Trénaunay-Weber syndrome. Laboratory results revealed hyponatremia (Na 119 mmol/L), hypokalemia (K 2.9 mmol/L), and low serum osmolality (247 mmol/kg). Urinary findings indicated elevated sodium (164 mmol/L) and osmolality (328 mmol/kg), confirming SIADH secondary to carbamazepine and hypokalemia due to corticosteroid therapy. Treatment included discontinuation of carbamazepine, fluid restriction, and potassium correction. One week post-discharge, the patient's electrolytes normalized (Na 138 mmol/L, K 4.6 mmol/L), and her symptoms resolved.[10]

Prakash et al. 2016, conducted a case study in 61-year-old female weighing 38 kg was scheduled for debridement and skin grafting of a post-burn raw area on the right arm. Her medical history and physical

examination were unremarkable, with normal biochemical findings except for hyponatremia (serum sodium 128 mEq/L, potassium 4.3 mEq/L). She denied any gastrointestinal losses such as vomiting or diarrhea. Repeat evaluation confirmed persistent hyponatremia (serum sodium 129 mEq/L). On detailed inquiry, she revealed a 34-year history of epilepsy managed with carbamazepine, which was identified as the probable cause of the electrolyte imbalance. Management included increasing oral salt intake and restricting fluid consumption, resulting in normalization of electrolytes (serum sodium 142 mEq/L, potassium 4.1 mEq/L) before surgery. She underwent standard general anesthesia with thiopentone, fentanyl, midazolam, and vecuronium, and her intraoperative and postoperative course was uneventful. The patient was counseled regarding carbamazepine-induced hyponatremia and advised to follow up with her physician.[9]

Kuz and Glenn (2005) reported a case of a 44-year-old woman who developed acute hyponatremia followed by two tonic–clonic seizures after accidentally ingesting double her usual evening dose of carbamazepine (600 mg). Upon admission, her serum sodium level was 122 mEq/L, and she was treated with an intravenous infusion of 0.9% normal saline, which normalized her sodium to 136 mEq/L within 24 hours. Her carbamazepine concentration measured 8.6 µg/mL prior to admission and 11.3 µg/mL on arrival, decreasing to 5.6 µg/mL after discontinuation of the drug. Notably, she had experienced a similar episode six months earlier following an excessive intake of carbamazepine, suggesting a recurrent dose-dependent hyponatremic reaction to the medication.[11]

DISCUSSION

Carbamazepine is a well-established anticonvulsant and psychotropic medication widely used in the management of epilepsy, trigeminal neuralgia, and various psychiatric disorders. Despite its proven therapeutic benefits, it is associated with several adverse effects, one of the most significant being hyponatremia, an electrolyte imbalance that can have serious neurological consequences. Hyponatremia is defined as a serum sodium concentration below 136 mmol/L. It becomes clinically significant when sodium levels fall between 115 and 125 mmol/L and is considered severe below 115 mmol/L. Acute hyponatremia, developing within 48 hours, is particularly dangerous and may result in seizures, coma, or cerebral edema if not promptly addressed.[3,4,17] Although hyponatremia occurs in less than 1% of hospitalized patients, even mild reductions in serum sodium can disrupt neuronal and cellular function, leading to increased morbidity and mortality.[3,5] The causes of hyponatremia are multifactorial and include various medications—most notably diuretics, antiepileptics, and antipsychotics. Among antiepileptic drugs, carbamazepine, oxcarbazepine, and lamotrigine are most frequently implicated. The risk is particularly high in elderly individuals, females, those with psychiatric comorbidities, hypothyroidism, or low baseline sodium levels.[6,12]

Carbamazepine-induced hyponatremia is thought to result primarily from syndrome of inappropriate antidiuretic hormone secretion (SIADH)-like effects. The drug enhances the action of antidiuretic hormone (ADH) by increasing renal tubular sensitivity and promoting the expression of aquaporin-2 water channels in the collecting ducts, thereby increasing free water reabsorption. Some studies have suggested a peripheral mechanism, as elevated ADH levels are not consistently detected, supporting the hypothesis that carbamazepine may act directly on renal osmoreceptors or modify the hypothalamic set-point for water balance. The reported incidence of carbamazepine-induced hyponatremia varies widely, from 1.8% to 40%, depending on the study population and concurrent medication use. Most cases are asymptomatic or mild, with sodium levels ranging from 125–135 mmol/L, and are often detected incidentally during routine laboratory evaluation. However, severe cases resulting in seizures have been reported, such as a 52-year-old female who developed grand mal epilepsy secondary to carbamazepine-induced hyponatremia.[12] The likelihood of drug-induced hyponatremia increases with polypharmacy, especially in elderly patients, due to overlapping mechanisms of water retention and impaired sodium regulation.[13-14] Commonly implicated drugs include selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants, diuretics, and antipsychotics such as risperidone. In some cases, pharmacodynamic interactions may enhance carbamazepine's antidiuretic effects, as observed when used concomitantly with SSRIs like paroxetine.[18] Although carbamazepine monotherapy seldom causes clinically significant hyponatremia, clinicians should remain alert to this potential adverse effect, particularly in high-risk individuals or those receiving multiple medications affecting water balance. The Naranjo Adverse Drug Reaction Probability Scale has been applied in similar cases and often indicates a probable to highly probable causal relationship between carbamazepine and hyponatremia.[19] Management depends on severity. Mild or asymptomatic cases can often be managed by dose adjustment or careful monitoring, whereas severe hyponatremia necessitates drug discontinuation, electrolyte correction, and close clinical supervision.[15-16] In our case, the patient was asymptomatic despite a serum sodium concentration of 118 mmol/L, aligning with previous reports that many patients tolerate mild to moderate hyponatremia without overt neurological signs. The growing use of carbamazepine in both neurological and psychiatric conditions, coupled with an aging population and increasing rates of polypharmacy, underscores the importance of routine monitoring of serum sodium levels. Physicians should educate patients about early warning symptoms such as confusion, fatigue, dizziness, or seizures, and should periodically evaluate electrolyte

profiles, particularly during the initial months of therapy or after dose escalation.

CONCLUSION

Carbamazepine-induced hyponatremia is an underrecognized yet clinically important adverse effect. Awareness of risk factors, careful patient selection, and regular biochemical surveillance can help prevent severe complications. Strengthening physician vigilance and promoting public awareness regarding epilepsy and its management can contribute to improved safety and a reduction in the social stigma associated with the disorder.

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CONFLICT OF INTEREST: Nil.

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