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Oxcarbazepine - Induced Symptomatic Hyponatremia - A Case Report

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Abstract: ***Oxcarbazepine, a newer anti - epileptic drug, is a structural analogue of carbamazepine and is used to treat partial seizures. Though it is thought to be safer with relatively milder side effects than Carbamazepine, serious adverse events have been occasionally noted. One of those is oxcarbazepine - induced hyponatremia due to its direct action on renal tubules. The risk is especially high in elderly patients and those receiving anti - epileptic drug polytherapy and diuretics. Oxcarbazepine - induced hyponatremia is usually mild and responds to fluid restriction alone, but at times it may become severe enough to cause hospitalisation. Our case is a 68 - year - old gentleman with Parkinson disease and partial seizures on oxcarbazepine who presented with generalised tonic - clonic seizures and altered sensorium secondary to drug - induced hyponatremia.***

Keywords: Oxcarbazepine, Anti - epileptic drug, Hyponatremia, Seizures, Altered sensorium

1. Introduction

Oxcarbazepine is a newer anti - epileptic drug that has fewer drug interactions and a better side effect profile than carbamazepine. Though it is relatively safer than carbamazepine, with less frequent and milder side effects, serious adverse events leading to hospitalisation have been occasionally reported. We hereby report a case of oxcarbazepine - induced severe symptomatic hyponatremia that led to intensive care unit admission.

2. Case Description

A 68 - year - old man who is a known case of Parkinson's disease with epilepsy (partial seizures) presented to the ER with seizures and an altered sensorium. Seizures were generalised tonic - clonic in nature, as opposed to the usual partial seizures for which he is being treated. Current medications included Oxcarbazepine 300mg twice daily and Levodopa/Carbidopa 110 mg three times a day. Patient was drowsy at presentation and was responding intermittently to verbal commands with a GCS of 11/15. In the ER, vitals were stable except for mild hyperpnea and hypoxemia, which were corrected with low - dose supplemental oxygen. A neurological examination revealed a drowsy patient without any focal deficits. The systemic review was not significant except for occasional right basal crepitations. Patient was admitted and stabilised. Initial blood biochemistry showed RBS of 99 mg/dL, sodium of 119 mEq/L, urea of 16 mg/dL, creatinine of 0.97 mg/dL, and bilirubin of 0.8 mg/dL. The brain imaging was normal. All other parameters, including the ECG, chest X - ray, kidney, and liver function tests, remained normal.

A provisional diagnosis of metabolic seizures secondary to hyponatremia was made. A 3% NaCl infusion was given as a 100 - ml bolus.30 minutes later, the patient had another episode of seizure that was treated with Inj. Midazolam and a repeat bolus dose of 3% NaCl followed by a maintenance infusion for 24 hours with a target not exceeding 8–10 mEq of correction per liter. No further seizures occurred during the hospital stay. Hyponatremia was evaluated as per the protocol, and pseudohyponatremia was ruled out. Further investigations revealed a serum osmolality of 215 mOsm/L, a urine osmolality of 300 mOsm/L, spot urine sodium of 60.4 mEq/L, a serum TSH of 5.86 mIU/L, and a serum cortisol of 9.89 mcg/dL.

Oxcarbazepine - induced syndrome of inappropriate ADH secretion (SIADH) was diagnosed based on clinical suspicion. After 24 hours of ICU stay and sodium correction, there was significant clinical improvement, and no further seizures occurred. Oxcarbazepine was discontinued, and the patient was advised to follow a fluid restriction. Daily serum sodium levels showed a progressive increase by day 9 of hospitalisation. An alternative anti - epileptic medication was started. Patient was discharged with a serum sodium level of 132 mEq/L. His sodium levels remained normal at the 1 - month follow - up.

3. Discussion

Hyponatremia is defined as a decrease in the serum sodium concentration to a level below 135 mmol per litre[1]. It has been described as the most common electrolyte imbalance, with a mortality rate ranging between 5 and 50% depending on the severity and acuity of onset 2. Various homeostatic mechanisms work in the body to maintain a stable plasma sodium concentration, of which the osmoreceptor - anti - diuretic hormone (ADH) system is an important one. In low - volume states, decreased firing of osmoreceptors stimulates the release of ADH, which helps in facilitated water reabsorption in the collecting ducts via aquaporin channels[3]. Many diseases and drugs cause inappropriate secretion of ADH in the absence of hypovolemia, leading to hyponatremia, an entity termed the Syndrome of Inappropriate ADH secretion (SIADH). SIADH is one of the most common causes of hyponatremia, especially in ICU

patients[4, 5]. Head injury, neurological illnesses such as stroke, solid organ malignancies, particularly small cell lung cancer, infections such as pneumonia and tuberculosis, pulmonary diseases such as Chronic Obstructive Pulmonary Disease and pneumothorax, and other factors are common causes of SIADH5. Drugs implicated in SIADH include Chlorpropamide, Tricyclic antidepressants, Selective Serotonin Reuptake Inhibitors, Monoamine oxidase inhibitors, Vincristine, Phenothiazines, Carbamazepine.

Oxcarbazepine is a 10 - keto analogue of carbamazepine that acts primarily by blocking voltage - gated sodium channels and thereby stabilising the neuronal membrane[6, 7]. It differs from carbamazepine in that it is not metabolised to an epoxide derivative, which is responsible for most adverse reactions and drug interactions[8, 9]. Oxcarbazepine is currently licensed for use in partial seizures with or without secondary generalisation. Its wider use in generalised epilepsy, neuropathic pain, and bipolar disease is being explored[10]. The side effect profile is similar to carbamazepine, but milder and less common11. The most common side effects include headache, fatigue, ataxia, dizziness, nausea, and vomiting. Another common side effect that causes the drug to be discontinued is skin rash12. Oxcarbazepine is also known to cause hyponatremia at a greater frequency than carbamazepine in a dose dependent manner. In a study conducted by Sachdeo, R et al., the incidence of severe hyponatremia (less than 125 mmol/l) was only 2.7%, and it was generally asymptomatic and of no clinical significance13.

Oxcarbazepine - induced hyponatremia has not been well characterised. Several mechanisms have been proposed including, increase in ADH secretion (SIADH) [14], increased sensitivity to ADH[15 - 17] and direct stimulation of collecting tubule V2 receptor - G protein complex independent of anti - diuretic hormone[18]. According to Sachdeo RC et al., after a water load, patients on oxcarbazepine had diminished free water clearance without a concomitant increase in serum ADH levels, indicating a probable direct effect of oxcarbazepine on renal tubular cells[19]. Oxcarbazepine - induced polydipsia20 is a less frequently mentioned mechanism.

A multivariate analysis conducted by Kim YS et al. showed that age, polytherapy with anti - epileptic drugs, and concomitant use of diuretics were independent risk factors for oxycarbazepine - induced hyponatremia[22]. The use of thiazide diuretics carries an especially high risk23. Studies recommend regular serum sodium monitoring in patients with advanced age, concomitant other anti - epileptic drugs, or diuretic usage[14, 22]. Sudden death in Epilepsy (SUDEP) and SIADH were reported in two patients taking Oxcarbazepine and Vigabatrin 24 by Robert Kostler et al. Though hyponatremia is a common chronic complication of oxcarbazepine, acute intoxications leading to hyponatremia have been identified[15, 21]. Most patients respond to fluid restriction alone, although a few cases, especially with acute intoxication, may need a short course of ADH antagonists like Tolvaptan.

4. Conclusion

Though oxcarbazepine - induced hyponatremia is milder in most instances, severe symptomatic hyponatremia requiring ICU admission has been reported. Hence, in routine clinical practice, serum sodium monitoring is recommended if there are risk factors like old age or concomitant use of other anti - epileptic drugs or diuretics, so as to recognise hyponatremia early before the symptoms set in.

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