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Frequency of and risk factors for oxcarbazepine-induced severe and symptomatic hyponatremia

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ABSTRACT

Purpose: Hyponatremia is one of the most common adverse effects in patients treated with oxcarbazepine (OXC). Most patients with OXC-induced hyponatremia are asymptomatic, so the presence of severe or symptomatic hyponatremia, which requires electrolyte correction or discontinuation of OXC therapy, has more important clinically implications. However, data for OXC-induced severe and symptomatic hyponatremia are limited.

Methods: We reviewed medical records of all patients with epilepsy who were treated with OXC at the Seoul National University Hospital. We analyzed serum sodium level results and attempted to identify correlations between various factors and the frequency of severe and symptomatic OXC-induced hyponatremia.

Results: Data from a total 1009 patient were examined. The frequency of severe and symptomatic hyponatremia was 11.1% and 6.8%, respectively. Multivariate analysis revealed that age ($P = 0.014$, OR 1.014), antiepileptic drug (AED) polytherapy ($P = 0.040$, OR 1.540), and the concomitant use of diuretics ($P < 0.001$, OR 5.597) were independent risk factors for OXC-induced severe hyponatremia. Age ($P = 0.001$, OR 1.034) and the concomitant use of diuretics ($P = 0.035$, OR 2.222) were independent risk factors for OXC-induced symptomatic hyponatremia. The frequency of OXC-induced symptomatic hyponatremia that was judged to be clinically significant was 2.8% among the total OXC-treated epilepsy patients.

Conclusion: Our study recommended that serum sodium be monitored regularly in patients taking OXC, especially in old age, AED polytherapy or concomitant use of diuretics, to assist in the early recognition of hyponatremia and to increase the awareness of symptoms that might be attributable to this.

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1. Introduction

As a keto-analog of carbamazepine (CBZ), oxcarbazepine (OXC) was developed to improve the side-effect profile of CBZ without affecting its antiepileptic potency. Many clinical trials have shown that OXC is a valuable antiepileptic drug (AED) for treating adults and children with partial seizures, as both monotherapy and adjunctive therapy.[1] Although structurally related to CBZ, OXC has several clinical advantages, such as more favorable pharmacokinetics and better tolerability; however, it is associated with an increased risk of developing hyponatremia.[2,3] OXC-induced hyponatremia is mostly asymptomatic, but its frequency is highly variable and has been estimated at 23–73.3%.[4] Nonetheless, data on the frequency and risk factors for clinically important OXC-induced severe and symptomatic hyponatremia are limited, and there are few studies on the possible effects of concomitant use of other AEDs and other drugs for the management of nonepileptic conditions on the development of hyponatremia.

We conducted this study to examine the frequency of severe and symptomatic hyponatremia and to identify its risk factors. We also evaluated the clinical characteristics of patients with hyponatremic symptoms and the approximate time point of their onset.

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2. Methods

2.1. Study design

We reviewed electronic medical records of all patients with epilepsy who were treated with OXC at the Seoul National University Hospital during a 10-year period from January 1, 2002 to December 31, 2011. The current study was approved by the Institutional Review Board of the Seoul National University Hospital.

2.2. Patients

Inclusion criteria were as follows: (1) adult patients with epilepsy aged 18 years or older; (2) history of OXC prescription; and (3) documentation of serum sodium levels at least once after OXC therapy. Exclusion criteria were as follow: (1) patients with disease likely to cause hyponatremia including renal failure, hypothyroidism, adrenal insufficiency; (2) patients with abnormal creatinine level; (3) patients with taking OXC for nonepileptic disorders. The baseline characteristics of patients including age, sex, age at seizure onset, disease duration, dosage of OXC, serum sodium levels, other concomitant AEDs, and other concomitant medical drugs.

2.3. Measurement of serum sodium levels and diagnosis of hyponatremia

A sodium level $\leq$134 mEq/L was defined as hyponatremia, and a level $\leq$128 mEq/L was defined as severe hyponatremia.[5,6] The combination of the presence of a sodium level $\leq$134 mEq/L and symptoms caused by reduced sodium led to a definition of symptomatic hyponatremia. Hyponatremic symptoms were classified into mild symptoms (lethargy, headache, dizziness, nausea, vomiting, restlessness, and disorientation) and significant symptoms (seizure aggravation, respiratory failure, and death).[7]

2.4. Comparison of medications

In patients who used OXC together with other AEDs (i.e., polytherapy), we analyzed the possible effects of other AEDs, including valproic acid (VPA), levetiracetam (LEV), topiramate (TPM), lamotrigine (LTG), zonisamide (ZNS), pregabalin (PGB), gabapentin (GBP), vigabatrin (VGB), clobazam, phenobarbital (PB) and phenytoin (PHT) on the development of hyponatremia.

We also assessed the possible effects of concomitant medications that are commonly prescribed for nonepileptic conditions, such as aspirin, nonsteroid anti-inflammatory drugs (NSAIDs), tricyclic acid (TCAs), serotonin-selective reuptake inhibitors (SSRIs), antipsychotics, diuretics, opioids, calcium channel blockers (CCBs), angiotensin II receptor blockers (ARB) and angiotensin-converting enzyme inhibitors (ACEI), all of which are also known to potentially cause hyponatremia.[7,8]

2.5. Statistical analysis

Statistical analysis was performed using SPSS version 19.0 for Windows (SPSS Inc., Chicago, IL). First, to compare demographic and clinical data between the two groups using three comparison situations (with or without hyponatremia with or without severe hyponatremia ($\leq$128 mEq/L), and with or without symptomatic hyponatremia), categorical variables were assessed using the χ^2 test, and continuous variables were compared using Student's t test. The significance level was set at $P < 0.05$. Subsequently, variables that reached statistical significance were entered into a binary forward-stepwise analysis. Thus, confounding variables were controlled. This was followed by the calculation of the odds ratios (ORs) and 95% CI.

3. Results

Our study included 1344 epilepsy patients who had been prescribed OXC. 335 patients were excluded for various reasons, such as absence of sodium level values after OXC treatment or insufficient follow-up (249 patients, 74.3%), prescription of OXC for a psychiatric disorder or pain control (45 patients, 13.4%) and having other medical diseases that caused hyponatremia (41 patients, 12.2%). As a result, 1009 patients were included in the present analysis. The mean duration of OXC treatment was 1280 $\pm$ 1236 (range, 39–4524) days. The mean period between start of OXC treatments and serum sodium measurements was 1031 $\pm$ 984 (range, 7–3427) days. The mean number of measurement serum sodium level per patients was 8.7 $\pm$ 7.5 (range, 1–78) times. The demographic and clinical data of each group (total number of patients, number of patients with severe hyponatremia, and number of patients with symptomatic hyponatremia) are listed in Table 1. The mean age of the patients was 51.55 $\pm$ 20.5 years and the sample included 565 men (55.9%). The mean age of patients with severe hyponatremia and symptomatic hyponatremia was 62.35 $\pm$ 15.5 and 65.23 $\pm$ 14.2 years, respectively. In our series, 112 (11.1%) and 69 (6.8%) patients were assigned to the severe hyponatremia and symptomatic hyponatremia groups, respectively.

A univariate analysis performed to identify risk factors for severe hyponatremia (Table 2) revealed that the following variables reached statistical significance: age, AED polytherapy, number of concomitant drugs, concomitant use of aspirin, concomitant use of NSAIDs, concomitant use of TCAs, concomitant use of diuretics, and concomitant use of CCBs. Multivariate analysis showed that age, AED polytherapy, and concomitant use of diuretics reached statistical significance as risk factors for developing severe hyponatremia. A univariate analysis that was performed to identify the risk factors for symptomatic hyponatremia (Table 3) revealed that the following variables reached statistical significance: age, number of concomitant drugs, and concomitant use of diuretics. Multivariate analysis showed that age and concomitant use of diuretics reached statistical significance as risk factors for developing symptomatic hyponatremia. Among the patients with symptomatic hyponatremia, 41 (4.1%) had mild symptom and 28 (2.8%) had significant symptom. Significant hyponatremic symptoms included seizure aggravation (26 patients) or respiratory distress (2 patients), and mild hyponatremic symptoms included lethargy (10 patients), headache (5 patients), dizziness (5 patients), nausea or vomiting (7 patients), altered mentality (8 patients), and abnormal behavior (6 patients). Among the patients with symptomatic hyponatremia, the mean duration of OXC therapy was 872.03 $\pm$ 859.1 (range, 373–2722) days. Hyponatremic symptoms occurred in 59.4% of patients within 2 years after initial OXC treatment. Thereafter, the frequency of symptomatic hyponatremia had relatively even distribution (Fig. 1).

4. Discussion

Although most cases of OXC-induced hyponatremia are asymptomatic and can be easily corrected,[1,9] severe or symptomatic hyponatremia is associated with various types of neurological damage, including seizures, altered mentality, brain stem herniation, and death.[7] The objectives of the current study were to estimate the frequency of severe and symptomatic hyponatremia and to identify risk factors for their development. We also attempted to examine the clinical presentation and the time of onset of hyponatremia. In addition, we attempted to identify the

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