Risk Factors of Oxcarbazepine-Induced Hyponatremia in Patients With Epilepsy

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Objectives: To determine the risk factors for hyponatremia in patients with epilepsy treated with oxcarbazepine (OXC).

Methods: Seventy-three adult patients with epilepsy aged older than 17 years who received OXC therapy were enrolled in this study. Patients who had hyponatremia due to any etiology before OXC therapy and patients receiving OXC therapy for nonepileptic disorders were excluded from this study. The baseline level of serum sodium of the patients was measured before the OXC therapy. During OXC therapy, serum sodium levels were measured at least once per 3 months.

Results: The frequency of hyponatremia (Na^+, ≤134 mEq/L) was 24.7% (n = 18) in patients with OXC therapy, and 8.2% (n = 6) of the patients had severe hyponatremia (Na^+, ≤128 mEq/L). The degree of decline in serum sodium concentration was significantly negatively correlated with the dosage of OXC. An increase of 1 mg in the dosage of OXC increased the risk of hyponatremia by 0.2%. Moreover, increasing the number of combination antiepileptic drugs increased the risk of hyponatremia.

Conclusions: Higher dosages of OXC and the number of combination antiepileptic drugs may increase the risk of OXC-induced hyponatremia in patients with epilepsy. Most patients are asymptomatic, but if symptoms of hyponatremia, such as headache, general malaise, gait disturbance, and somnolence, are suspected, the serum sodium level should be measured; it may be necessary to decrease the OXC dose or to discontinue the drug.

Key Words: oxcarbazepine, hyponatremia, epilepsy, risk factor, dosage

(*Clin Neuropharm* 2010;33: 293–296)

Epilepsy is a common neurological disorder with a prevalence of 0.5% to 1% in the general population.[1] It often is a chronic medical problem requiring long-term antiepileptic drug (AED) therapy.[2] Seizures in many patients do not remit despite appropriate medication, and lifelong AED therapy is usually required for those with refractory epilepsy.[2,3] This practice poses a medical dilemma because prolonged AED therapy can be associated with a wide range of chronic adverse effects.[2,4] The past decade has brought many advances to the treatment of epilepsy, including many newer pharmacological agents. Newer AEDs have not generally been more effective than the older AEDs, but some, at least, may be better tolerated with fewer adverse effects and with minimal drug interactions.[5] Some also have a broad spectrum of activity.[5] However, our knowledge concerning the safety profiles of newer AEDs is not adequate because of the relatively short time these drugs have been on the market.[5]

Oxcarbazepine (OXC) is a new generation AED that can be used as monotherapy or combination therapy in the treatment of epilepsy.[6–10] Because OXC is a 10-keto analogue of carbamazepine, its mechanisms of action and adverse effects are similar to carbamazepine.[7] The most commonly reported adverse events associated with OXC are usually related to central nervous or gastrointestinal systems, including dizziness, nausea, headache, somnolence, diplopia, and fatigue.[6–10] Hyponatremia has been recognized to be one of the adverse effects of OXC.[6,11,12] It had been suggested that OXC may have a higher risk of developing hyponatremia when compared with carbamazepine.[12,13] Whereas hyponatremia induced by OXC therapy is mostly asymptomatic, the prevalence is highly variable and estimated to be 23% to 73.3%.[13–16] From 14 studies of OXC therapy, serum sodium levels less than 135 mEq/L were noted in 21.5% of patients and less than 125 mEq/L in 2.7% of patients.[7] Approximately 1% of patients with OXC-induced hyponatremia requires changing the regiment.[14] Therefore, hyponatremia may be an unrecognized adverse effect in patients with epilepsy who receive OXC therapy. In this study, we analyzed the risk factors for hyponatremia in patients with epilepsy who received OXC treatment for seizure control.

MATERIALS AND METHODS

Subjects

This is a single-center, observational study. From August 2005 to July 2009, 73 adult patients with epilepsy were enrolled into this study. The study hospital, Chang Gung Memorial Hospital-Kaohsiung, is a medical center and a main referral hospital that serves an area with 3 million inhabitants in southern Taiwan. Patients aged older than 17 years and who were receiving OXC monotherapy or combination therapy were enrolled in this study. The institutional ethics committee approved the study protocol. The enrolled patients were treated with OXC for seizure and received regular sodium follow-up at the study hospital. However, patients who had hyponatremia due to any etiology before OXC therapy and patients receiving OXC therapy for nonepileptic disorders were excluded from this study. All patients received a physical examination and interviews. The clinical records of the patients with epilepsy were reviewed, and the age of onset, type of seizure, etiology of seizure, dosage of OXC, associated medical diseases and medication use, and the number of current AEDs were recorded.

Assessment of Serum Sodium Level

Blood samples were taken between 8 and 10 AM after overnight fasting and analyzed by the central laboratory of

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The authors have no conflicts of interest to declare in relation to this study.

DOI: 10.1097/WNF.0b013e3181f80bd4

TABLE 1. Demographic Data of the 73 Patients With OXC Therapy

Characteristics	
Sex, n (%)	
Male	34 (46.6%)
Female	39 (53.4%)
Age (y)	38.8 ± 15.6
Age at seizure onset (y)	25.5 ± 20.1
Dose of OXC use (mg/d)	1000.7 ± 439.5
Baseline sodium level (mEq/L)	140.4 ± 2.2
Lowest sodium level (mEq/L)	137.7 ± 5.0
Seizure type, n (%)	
Partial	66 (90.4%)
Generalized	7 (9.6%)
Mode of AED therapy, n (%)	
OXC monotherapy	25 (34.2%)
Combination therapy	48 (65.6%)
Associated medical diseases	
Diabetes mellitus	2
Hypertension	8
Cerebrovascular disease	12
Brain tumor	4

Values are expressed in mean ± SD unless otherwise indicated.

Chang Gung Memorial Hospital-Kaohsiung for serum levels of sodium, aspartate transaminase, alanine transaminase, and creatinine. The baseline level of serum sodium of the patients was measured before OXC therapy. After OXC therapy, serum sodium levels were measured at least once per 3 months. A sodium level lower than and equal to 134 mEq/L was defined as hyponatremia, and a level lower than and equal to 128 mEq/L was defined as severe hyponatremia.[12,15] The degree of change in serum sodium concentration also was calculated and defined as the lowest serum sodium level after OXC therapy minus the baseline sodium level.

Statistical Analyses

Three separate series of statistical analyses were performed using the SAS software package (version 9.1; SAS Statistical Institute, Cary, NC). First, to compare demographic data between the 2 patient groups (with or without hyponatremia), categorical variables (sex, associated medical diseases and medication use, and the number of current AEDs being used) were assessed using χ^2 or Fisher exact tests, and continuous variables (age and dosage of OXC used) were compared using the Student t test. Second, significant variables ($P < 0.05$) found to be associated with hyponatremia were entered into a forward stepwise logistic regression analysis model, which allows for simultaneous control of multiple factors. All statistical tests were 2 tailed. Third, correlation analysis was used to explore the relationship between the degree of change in blood sodium concentration and variables. Receiver operating characteristic

TABLE 2. Comparisons of Demographic Data and Risk Factors Between Patients With Normal Natremia and Hyponatremia

	Normal Natremia (n = 55)	Hyponatremia (n = 18)	*P*	Odds Ratio	95% CI
Sex					
Male	26	8	1.000	0.892	0.306–2.601
Female	29	10	1.000	1.121	0.384–3.267
Age, y	37.6 ± 16.0	39.8 ± 15.0	0.598		
Age at seizure onset, y	25.7 ± 20.4	25.0 ± 19.7	0.907		
Dosage of OXC, mg/d	913.6 ± 400.3	1266.7 ± 457.9	0.003		
Creatine level, mg/dL	0.90 ± 0.27	0.84 ± 0.25	0.444		
Etiology classification					
Symptomatic	30	7	0.287	0.530	0.179–1.572
Idiopathic or cryptogenic	25	11	0.287	1.886	0.636–5.587
Associated medical diseases					
Diabetes mellitus	2	0	1.000	0.764	0.652–0.855
Hypertension	6	2	1.000	1.021	0.187–5.571
Cerebrovascular disease	10	2	0.718	0.563	0.111–2.848
Brain tumor	3	1	1.000	1.020	0.099–10.463
Associated medications					
Antihypertensive drug	6	2	1.000	1.021	0.187–5.571
Diuretic	2	2	0.253	3.313	0.432–25.428
Oral hypoglycemic agent	2	0	1.000	1.395	0.120–16.276
Antiplatelet drug	2	0	1.000	1.395	0.120–16.276
Statin	2	1	1.000	1.559	0.133–18.279
No. AED therapy	1.9 ± 0.8	2.4 ± 1.1			
4 AEDs	1	4			
3 AEDs	15	4	0.043		
2 AEDs	18	6			
OXC Monotherapy	21	4			

Values are expressed in mean ± SD unless otherwise indicated.

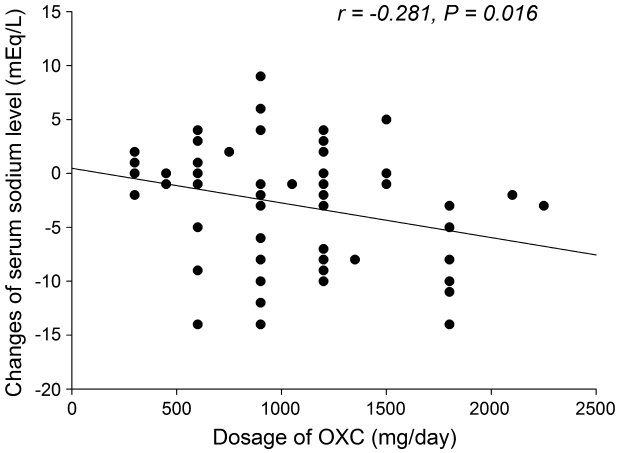

FIGURE 1. Relationship between the degree of change in blood sodium concentration and dosage of OXC in 73 patients with epilepsy.

(ROC) curves were generated for the dosage of OXC. The areas under the ROC curves were calculated for each parameter and compared.

RESULTS

The demographic data of all patients are listed in Table 1. The age at onset of seizures ranged from 1 month to 94 years. Approximately half of the patients had idiopathic or cryptogenic epilepsy, whereas the other patients experienced symptomatic etiologies that included cerebrovascular accident (n = 12), perinatal brain damage (n = 8), central nervous systemic infection (n = 7), head trauma (n = 5), and neoplasm (n = 4). Oxcarbazepine was titrated to a dose ranging from 300 to 2250 mg/d. The baseline sodium level ranged from 136 to 149 mEq/L. The change of serum sodium level ranged from −14 to 9 mEq/L. The frequency of hyponatremia (Na^+, ≤134 mEq/L) was 24.7% (n = 18), and 8.2% (n = 6) of the patients had severe hyponatremia (Na^+, ≤128 mEq/L). In patients with normal blood sodium, the dosage of OXC used ranged from 300 to 2100 mg/d. In patients with hyponatremia, the dosage of OXC used ranged from 600 to 2250 mg/d. Whereas most patients (n = 13) with OXC-induced hyponatremia were asymptomatic, 5 patients (27.8%) were symptomatic. The serum sodium levels among the asymptomatic subjects ranged from 127 to 134 mEq/L. In the symptomatic patients, the serum sodium level was relatively lower than that in the asymptomatic patients (124–127 mEq/L). Four patients (6.8%) discontinued OXC treatment because of intolerable side effects. The symptoms of OXC-induced hyponatremia included headache (n = 1), general malaise (n = 3), gait disturbance (n = 1), and somnolence (n = 1).

The comparative results of the clinical features between patients with or without hyponatremia are listed in Table 2. Statistical analysis between the 2 patient groups revealed the following significant findings: numbers of AEDs being used ($P = 0.04$) and the dosage of OXC ($P = 0.003$). Sex, age, serum creatine levels, etiology, associated medical diseases, and associated medications showed insignificance. Second, significant univariate factors and possible confounding factors used in stepwise logistic regression included numbers of AEDs being used and the dosage of OXC. The results revealed that after analysis of all the above-mentioned variables, the dosage of OXC was the only risk factor for the presence of hyponatremia, and an increase of 1 mg in dosage increased the risk of hyponatremia by 0.2% ($P = 0.003$, odds ratio = 1.002, 95% confidence interval [CI] = 1.001–1.003). The degree of change in blood sodium concentration was significantly negatively correlated with the dosage of OXC ($r = -0.281$, $P = 0.016$) (Fig. 1). To demonstrate the relationship between the dosage of OXC and the presence of hyponatremia in patients with epilepsy, ROC curves were generated for the dosage of OXC. The area under the ROC curve for the dosage of OXC was 0.720 ($P = 0.005$, 95% CI = 0.59–0.85). The cutoff value of the dosage of OXC for the presence of hyponatremia was 1125 mg/d (sensitivity of 70% and specificity of 70%).

DISCUSSION

We confirmed that hyponatremia often is an asymptomatic adverse effect in patients with epilepsy receiving OXC therapy. Furthermore, we demonstrated a novel observation that the degree of change in blood sodium concentration is significantly negatively correlated with the dosage of OXC. The cutoff value of the OXC dosage associated with the risk of hyponatremia in patients with epilepsy was 1125 mg/d.

Both carbamazepine and OXC are known to cause hyponatremia.[12,13] Carbamazepine has been proposed to have both central and peripheral effects on antidiuretic hormone that include the increased release of antidiuretic hormone from the neurohypophysis, increased kidney sensitivity to antidiuretic hormone, direct effect on the distal convoluted tubules, and prolonged vasopressin half-life by decreasing the effect of vasopressinase.[13,17] Oxcarbazepine is structurally related to carbamazepine, and it has shown similar hyponatremic effects. However, the frequency of hyponatremia in patients with OXC therapy is higher than that with carbamazepine.[12] The exact mechanism of OXC-induced hyponatremia is still uncertain. Some evidence has shown that OXC-induced hyponatremia is not attributable to the syndrome of inappropriate secretion of antidiuretic hormone.[18] Only peripheral renal effects have been proposed to be the cause of OXC-induced hyponatermia.[18] This recent study[18] suggested that the possible mechanisms of OXC-induced hyponatremia may be related to a direct effect of OXC on the renal collecting tubules or an enhancement of their responsiveness to circulating antidiuretic hormone.

In our patients, the frequency of hyponatremia associated with OXC therapy was 24.7%. Among them, 8.2% of the patients had a severe hyponatremia. The frequency of OXC-induced hyponatremia in our patients is similar to a recent report by Dong et al.,[12] where the frequency of hyponatremia was reported to be 29.9% among OXC-treated patients, and 12.4% of these patients experienced severe hyponatremia. Patients with OXC-induced hyponatremia are usually asymptomatic.[6,12,13] Most of our patients with hyponatremia also were asymptomatic. However, patients with symptomatic hyponatremia usually had a benign course and rapidly recovered after correction of serum sodium, such as salt supply. In patients with severe and symptomatic hyponatremia, it may be necessary to decrease the OXC dose or to discontinue the drug.

Whether the degree of decline of serum sodium level is related to the dosage of OXC is controversial. Emerging evidences[9,10,16] have shown that the decrease of sodium concentration induced by OXC is dose dependent. Beydoun et al.[9] demonstrated that lower sodium levels were noted in patients receiving a high dose of OXC (2400 mg/d) than in patients receiving a low dose (300 mg/d). In the present study, we noted that the decrease of mean serum sodium level from baseline was significantly negatively correlated with the dosage of OXC. An

increase of 1 mg in the dosage of OXC increased the risk of hyponatremia by 0.2%.

In the present study, an increased number of AEDs in combination with OXC was found to increase the risk of OXC-induced hyponatremia. The AEDs are notoriously known to have drug interactions between themselves and other medications.[19] Adjunctive treatment with levetiracetam has been observed to be associated with an increased risk of hyponatremia.[12] However, in the present study, it was difficult to identify the additional effect of any individual AED in OXC-induced hyponatremia because of the small number of patients in each group. Further studies are needed to confirm this observation.

The correlation of age and the incidence of hyponatremia associated with OXC is controversial.[11,12,15,20] It also has been suggested that elderly patients on concomitant natriuretic drugs is at significant risk of developing serum sodium levels below 135 mEq/L.[11] Our study did not show a significant correlation between age or diuretic use and hyponatremia. However, the number of cases in this study is limited, and further studies are needed to clarify this issue.

Sex also has been proposed to be a risk factor for drug-induced hyponatremia,[21] with female subjects being more prone to hyponatremia. The mechanism of the sex difference includes a higher sensitivity to endogenous arginine vasopressin, lower total body sodium concentration, lower urine excretion of sodium, lower mean value of intracellular sodium, and different sodium transport through cell membrane in women.[21] Whereas a study by Kutluay et al.[11] found that elderly women might have a greater magnitude of sodium decrease but without statistical significance, most reports have not concluded that there is a sex difference in OXC-induced hyponatremia.[8–10,12,18] Our results did not show a sex difference in OXC-induced hyponatremia. In our study, because of limited case number and relative few elderly patients, some issues could not be further clarified. Increase of case numbers may be mandatory in future studies to answer more relevant question such as the risk of OXC-related hyponatremia in elderly patient and sex. Also, questions of whether individual AEDs or other drugs may increase the risk of hyponatremia in this patient group.

In conclusion, the use of OXC in patients with epilepsy is associated with a dose-dependent reduction in serum sodium levels. Although most patients with OXC-induced hyponatremia are asymptomatic, some are symptomatic. If any patient taking OXC presents with symptoms, such as headache, general malaise, gait disturbance, and somnolence, the serum sodium should be measured promptly, and if hyponatremia is confirmed, the OXC dose should be decreased. In some patients with severe hyponatremia, it may be necessary to discontinue the OXC altogether.

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