Incidence and Predictive Factors of Hyponatremia in Acute Carbamazepine Exposure

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Abstract

Introduction: Hyponatremia, an electrolyte abnormality reported during long-term treatment with carbamazepine (CBZ), is increasingly observed in acute poisoning. It incidence and predictive factors varies from one study to another because of heterogeneity of studied patients and inclusion criteria.

Objective: We aimed to study the incidence of hyponatremia in CBZ poisoning in our specialized toxicological intensive care unit and to detect the factors associated to its occurrence.

Methods: Our study was observational spread over four years; from January 2010 to December 2013 including all symptomatic CBZ-poisoned patients admitted in the ICU with a plasma level of CBZ ≥ 12 mg/l for those who were being regularly treated with CBZ and ≥ 5 mg/l for those who are not. Co-ingestion cases were excluded.

Results: Eighty three patients were eligible with a mean age of 29.6± 12.6; there sex-ratio was of 0.49.

A history of psychiatric disease was noted in 57.8%, epilepsy in 9.6% and long-term treatment with CBZ in 53%. Hyponatremia was noted in 30 patients (36%) with a mean value of 132 ± 2.3 mEq/L. Among seven studied parameters (age, sex, supposed ingested dose, CBZ serum level, history of psychiatric disorders, history of epilepsy, long-term treatment with CBZ), the univariate analysis of risk factors associated to hyponatremia showed that only a history of psychiatric disorders (p=0.003) and long term CBZ treatment (p=0.000) were strongly predictors of hyponatremia. Multivariate analysis enhanced this results and proved a significant relationship between long-term CBZ treatment and hyponatremia (OR=11.18, CI95% (3.38; 36.96), p=0.000) and history of psychiatric disorders (OR= 4.63, CI95% (1.62; 1.32), p=0.003).

Conclusion: Although hyponatremia is common in acute CBZ poisoning, it remains under diagnosed, especially when it is asymptomatic. As it can be dangerous, it is imperative to regular ionogram control and stop treatment when it occurs.

INTRODUCTION

Carbamazepine (5H-dibenzazepine-5-carboxamide) is an iminostilbene derivative used as an anticonvulsant, also for relief of pain in trigeminal neuralgia and as a thymoregulator in bipolar affective disorder. Given these broad indications and its availability, carbamazepine (CBZ) is increasingly prescribed and accordingly involved in both accidental and voluntary poisoning [1]. The most common manifestations of CBZ overdose are generated by its neurological and cardiovascular toxicities [2]. As for the metabolic abnormalities, hyponatremia is the most recorded one. It is met in both acute and chronic exposure. The main mechanism involved is the syndrome of inappropriate antidiuretic hormone secretion (SIADH) [2,3]. As this electrolyte disturbance may be dangerous and lead to serious complications, we have done this work which aims to study the incidence of hyponatremia in CBZ poisoning and to detect the risk factors of its occurrence.

PATIENTS AND METHODS

The study design

We performed a retrospective observational study spread over four years; from January 2010 to December 2013, in a Tunisian 18-bed medical and toxicological intensive care unit (ICU), including all symptomatic CBZ-poisoned patients admitted in the ICU with a plasma level of CBZ ≥ 12 mg/l for those who were being regularly treated with CBZ and ≥ 5 mg/l
for those who are not. Blood CBZ measure was done by the Cobas Integra immunoassay. Hyponatremia was defined as a serum concentration of (Na+) below 135 mEq/L.

CBZ-poisoned patients with co-ingested substances were excluded.

Data were obtained from medical records. We collected parameters referring to poisoning circumstances (supposed ingested dose, delay of medical care, long-term treatment), clinical features and toxicological exams.

Statistical methods

All statistical analyses were performed using the Statistical Package for Social Science software (IBM SPSS, version 21.0).

For qualitative data, we calculated frequency distribution and relative frequency (Percent frequency). For quantitative data, we calculated means and standard deviation.

We compared categorical data with Pearson’s Chi-square Test. Differences between cases and controls in continuous variables were compared using Student’s unpaired t-test. The p value < 0.05 was considered statistically significant.

Risk factors of hyponatremia were determined by calculating the Odds ratio (OR) via logistic regression. Data are depicted together with their 95% confidence intervals (95% CIs).

RESULTS

A total of 234 patients were exposed to CBZ among 4780 admissions for acute poisoning; which represents 4.6% of total admissions for acute poisoning. Only 83 patients were included (Figure 1).

They were aged of 29.6 ± 12.6 years with a sex-ratio of 0.49. A history of psychiatric disease was noted in 57.8%, epilepsy in 9.6%, and long-term treatment with CBZ in 53% with a median duration of CBZ treatment of 7 years (1 month; 30 years). The supposed ingested dose was of 3.2 g (0.8; 20) and the delay between ingestion and hospital arrival was of 6.4 ± 5.6 hours.

Initial physical exam showed coma in 35% of cases (n=29), agitation in 24% (n=20), dysarthria in 9.6% (n=8), seizures in one patient and dizziness in another. Hypotension was present in four patients, tachycardia in 25 (30%) and atrioventricular block in 4 patients. The initial serum CBZ level was of 17 mg/L (11; 35).

Demographic and clinical features are displayed in Table (1).

Hyponatremia was noted in 30 patients (36%) with a mean (Na+) concentration of 132 ± 2.3 mEq/L and a normal urinary density. Mechanical ventilation was required for 36 patients (43%), fluid expansion for 66 patients (79%) with a mean isotonic saline solution infusion of 1590 ± 780 ml, isoproterenol support in one patient and norepinephrine in another. Activated charcoal was administered to 30 patients (36%) as a bolus of 50g in all cases and as repeated doses in 12 cases. The duration of mechanical ventilation was 20 ± 39 hours. All patients were discharged from ICU to home or psychiatric structure in a delay of 37 h (11; 352).

The univariate analysis of risk factors associated to hyponatremia showed that among seven studied parameters (age, sex, supposed ingested dose, history of psychiatric disease, history of epilepsy, CBZ long term treatment and (CBZ) serum level), only the history of psychiatric disease (p=0.003) and long-term CBZ treatment (p=0.000) were strongly predictive of hyponatremia as it is shown in Table (2).

Multivariate analysis showed a significant relation between long-term CBZ treatment and hyponatremia (OR=11.18, CI95% (3.38; 36.96), p=0.000) and history of psychiatric disorders (OR=4.63, CI95% (1.62; 1.32), p=0.003).

DISCUSSION

Carbamazepine is known to cause clinically meaningful drug interactions since it is an enzymatic inducer. Acute CBZ poisoning can be responsible of arrhythmia, coma, and seizures even in non-epileptic persons and may increase seizures occurrence in persons with epilepsy [4], because of the neurotoxic effect of its metabolite (5,6) which can lead to serious complications such as permanent brain damage [7,8].

The diagnosis of drug-induced hyponatremia is based on the history of specific drug use and the correction of this metabolic disturbance after stopping the offending substance [9]. Hyponatremia is commonly described with CBZ. It usually occurs in chronic CBZ treated patients and most often within the first 3 months of therapy [10, 11]. CBZ led to hyponatremia in patients with epilepsy, neuralgia, mental retardation, and psychiatric disorders with a frequency varying between 4.8 and 40% [12]. Its frequency was of 36% in our study.

Hyponatremia associated with CBZ exposure is mainly explained by the antidiuretic effects of CBZ [13-15]. Basic science and mechanistic research indicate that “in contrast to patients with a reset osmostat, who have a normal water loading test, CBZ induces an abnormal water loading test with higher urine osmolalities than in control subjects or in patients with central diabetes insipidus [16-18]. Plasma ADH was unchanged from baseline when the subjects were hyponatremic after water loading, suggesting that there was a resetting of the hypothalamic osmostat [17,18]. The higher urine osmolalities during the water loading test at a time when plasma ADH levels remained unchanged or unmeasurable in another study from baseline suggested increased ADH action in the distal tubule [16-18]. This increase in CBZ-induced activity of ADH in the distal tubule appears to be due to an upregulation of aquaporin 2 expression [19]. The hyponatremia associated with CBZ is, therefore, an altered sensitivity of the hypothalamic osmoreceptors (reset
osmostat) and/or due to an upregulation of aquaporin 2 
expression to increase distal tubular action of ADH [16-19].
Moreover, the hyponatremia associated with CBZ is not due to 
the syndrome of inappropriate section of ADH or to renal salt 
wasting. Some specific risk factors for hyponatremia have been 
explored in several clinical studies, including an age more than 40 
years, concomitant use of a substance generating hyponatremia, 
history of surgery and female gender [11,15]. However, minimal 
consensus has been found regarding both dosage/level of CBZ 
and polymedication [13,20]. Psychiatric condition is known to 
increase the risk of hyponatremia. Its occurrence in psychiatric 
settings is a complex and multifactorial phenomenon that may 
occur following an adverse drug reaction as well as in close 
relationship with some diagnoses as polydipsia in schizophrenia 
[21]. In our study, both a history of psychiatric disorders (OR=4.63, 
CI95% (1.62; 1.32), p=0.003) and a long term treatment with 
CBZ (OR=11.18, CI95% (3.38; 36.96), p=0.000) were strongly 
associated with hyponatremia, but never with CBZ serum level, 
or others signs of poisoning as neurological or cardiovascular 
symptoms. According to our knowledge, the occurrence of 
hyponatremia in psychiatric disorders is often associated with 
hypotonic urine due to potomania. This mechanism could not be 
retained in our patients because of their normally concentrated 
urine. Moreover, the persistence of hyponatremia in most of 
cases in spite of the decrease of the CBZ serum level invoked the 
chronicity of this phenomenon and encouraged replacing CBZ by 
another drug.

CONCLUSION

Although hyponatremia is common in acute poisoning, it 
remains under diagnosed even if its prevalence was 36% in 
our study which concerned acute exposure. Hyponatremia is 
often asymptomatic, but it can be dangerous and lead to serious 
complications such as brain damage and seizures. As it has a 
high prevalence in long-term treated patients, it is imperative 
to recommend a regular ionogram control since the initiation of 
CBZ treatment in order to detect this disorder and correct it. Its 
persistence or its aggravation imposes the discontinuation of the 
incriminated treatment.

Our study suffers from some limits such as its retrospective 
character and its limited sample.

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