SciMedCentral

Journal of Pharmacology & Clinical Toxicology

Research Article

Incidence and Predictive Factors of Hyponatremia in Acute Carbamazepine Exposure

Brahmi Nozha*, Khzouri Takoua, Essafi Fatma, Mezghenni Mohamed, M'rad Aymen, Amamou Mouldi, and Nabil Ben Salah

Department of Intensive Care and Toxicology, Centre Mahmoud Yaacoubd'Assistance Médicale Urgente, Tunisia

***Corresponding author**

Brahmi Nozha, Department of Intensive Care and Toxicology, Centre Mahmoud Yaacoubd'Assistance Médicale Urgente- CAMU, 50 Rue Abou Kacem Chebbi, 1089 Montfleury, Tunis-Tunisia, Tel: 698645755/671249029; Email: nozha_brahmi@yahoo.fr

Submitted: 09 January 2017

Accepted: 11 February 2017

Published: 15 February 2017

ISSN: 2333-7079

Keywords

- Carbamazepine
- Exposure
- Hyponatremia
- Psychiatric disease

Abstract

Introduction: Hyponatremia, an electrolyte abnormality reported during long-term treatment with carbamazepine (CBZ), is increasingly observed in acute poisoning. Its incidence and predictive factors varies from one study to anotherbecause 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 toDecember 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 CBZmeasure 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 examshowed 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,a mean plasma osmolarity level of 271 ± 5.2 mosol/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 asrepeated 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

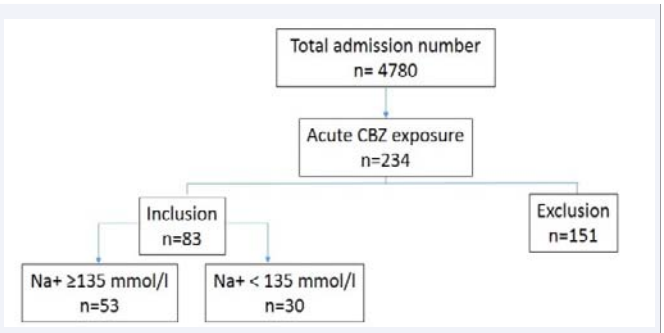

Figure 1 Distributions of admissions accoding to inclusion criteria.

(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

Table 1: Clinical ad biological characteristics of Patients.

	GCS	SBP mmHg	HR bpm	[Na+] mEq/L	[CBZ]H0 mg/L	ICU lengthstay (h)
Mean	11.36	115.8	87.35	136	18.07	55.9
Mediane	13.00	114	84	136	17.3	37
Standard deviation	3.7	17.5	15.8	3.8	7.57	57.11
Minimum	3	70	45	125.3	11	11
maximum	15	150	120	148	35	352

GCS : glasgow coma scale, SBP : systolic blood pressure, HR : heart rate, CBZ : Carbamazepine

Table 2: Univariate analysis of hyponatremia risk factors.

	G1 Natremia<135 30 (36%)	**G2** Natremia≥135 53 (64%)	*P*
Age (years)	31.5 ±12	28.6 ±12.5	0.33
Male sex	23 (76.6%)	18 (34%)	0.08
History of psychiatricdisorders	23 (76.6%)	24(45%)	**0.003**
History of epilespsy	5 (16%)	3 (5%)	0.09
Long-term CBZ treatment	25 (83%)	19 (35.8%)	**0.000**
the supposed ingested dose (mg)	5.25 ±4.9	3.29 ±1.77	0.056
Carbamazepineserumlevel (H0)	22 ±9.5	23± 6	0.6

G1 : group hyponatremia (+), G2 : group hyponatremia (-)

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.

REFERENCES

1. Peces R, Azorin S, Peces C. Extended hemoperfusion in the treatment of acute carbamazepine intoxication. Nefrologia. 2010; 30: 127-130.
2. Koraichi EA, Mounir K, Haddoury EM. Prise en charge d'une intoxication à la carbamazépine en réanimation pédiatrique. Archives de Pédiatrie. 2011; 18: 97-98.
3. Bonilha L, Collares CF, Do Amaral DA, DantasBarcia S, De Almeida Oliveira AM, Li LM. Antiepilepticdrugs: astudy of 1028 cases registered by the Sao Paulo Intoxication Control Center.Seizure. 2005; 14:170-174.
4. Ahmad Y, Nastaran E-M, Marzieh S, Gholamreza M, Lejla Z, Sabzghabaee MA. Risk factors and the outcome of therapy in patients with seizure after Carbamazepine poisoning: A two-year cross-sectional study. J Res Pharm Pract. 2015; 4: 18-23.
5. Clemens B, Ménes A, Nagy Z. Objective assessment of neurotoxicity while shifting from carbamazepine to oxcarbazepine. ActaNeurol Scand. 2004; 109: 324-329.
6. Kuz GM, Manssourian A. Carbamazepine-induced hyponatremia: Assessment of risk factors. Ann Pharmacother. 2005; 39:1943-1946.
7. Holtschmidt-Täschner B, Soyka M. Hyponatremia-induced seizure during carbamazepine treatment. World J Biol Psychiatry. 2007; 8: 51-53.
8. Arieff AI, Ayus JC, Fraser CL. Hyponatremia and death or permanent

brain damage in healthy children. Brit Med J. 1992; 304: 1218-1222.

9. Liamis G, Milionis H, Elisaf M. A review of drug-induced hyponatremia. Am J Kidney Dis. 2008; 52: 144-153.

10. Kuz GM, Manssourian A. Carbamazepine-induced hyponatremia: assessment of risk factors. Ann Pharmacother. 2005; 39: 1943-1946.

11. Asconapé JJ. Some common issues in the use of antiepileptic drugs. Semin Neurol. 2002; 22: 27–39.

12. Van Amelsvoort T, Bakshi R, Devaux CB, Schwabe S. Hyponatremia associated with carbamazepine and oxcarbazepine therapy: a review. Epilepsia. 1994; 35: 181-188.

13. Gandelman MS. Review of carbamazepine-induced hyponatremia, Prog NeuropsychopharmacolBiol Psychiatry.1994; 18: 221-233.

14. Jouko I, Isojarvi T, Usko E, Huuskonen J, Arto J. Pakarinen et al. The Regulation of Serum Sodium after Replacing Carbamazepine with Oxcarbazepine. Epilepsia. 2001; 42: 741-745.

15. Lange-Asschenfeldt C, Kojda C, Cordes J, F Hellen, Gillmann A, Grohmann R et al. Epidemiology, Symptoms, and Treatment Characteristics of Hyponatremic Psychiatric Inpatients. J Clin Psychopharmacol. 2013; 33: 799-805.

16. Meinders AE, Ceika V, Robertson GL. The antidiuretic action of carbamazepine in man. Clin Sci Mol Med.1974; 47: 289-299.

17. Sachdeo RC, Wasserstein A, Mesenbrink PJ, D'Souza J. Effects of oxcarbazepine on sodium concentration and water handling. Ann Neurol. 2002; 51: 613-620.

18. Stephens WP, Coe JY, Baylis PH. Plasma arginine vasopressin concentrations and antidiuretic action of carbamazepine. Br Med J. 1978; 1:1445-1447.

19. De Braganca AC, Moyses ZP, Magaldi AJ. Carbamazepine can induce kidney water absorption by increasingaquaporin 2 expression. Nephrol Dial Transplant 2010; 25: 3840-3845.

20. Staniszewska A, Burda P, Waldman W, Anand JS. Correlation between carbamazepine serum level and clinical condition of acute poisoned patient. Przegl Lek. 2009; 66: 279-281.

21. Siegel AJ. Hyponatremia in psychiatric patients: update on evaluation and management. Harv Rev Psychiatry. 2008; 16: 13-24.

Cite this article

Nozha B, Takoua K, Fatma E, Mohamed M, Aymen M, et al. (2017) Incidence and Predictive Factors of Hyponatremia in Acute Carbamazepine Exposure. J Pharmacol Clin Toxicol 5(1):1067.