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OXCARBAZEPINE INDUCED HYPONATREMIA: A POTENTIAL EXPLANATION OF ITS PHYSIOPATHOLOGY.

Carlos G. Musso¹⁻³, Vilas M¹⁻³, Aparicio C¹, Bevione P¹,
Reynaldi J¹, Rojas J², Jauregui R³, Algranati L¹.

¹Nephrology and ² Neurology Departments.
³ Centro Médico Agustin Rocca
Hospital Italiano de Buenos Aires.
Buenos Aires. Argentina

[carlos.musso @ hospitalitaliano.org.ar](mailto:carlos.musso@hospitalitaliano.org.ar)

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SUMMARY

Carbamazepine and oxcarbazepine are antiepileptic drugs which can induce hyponatremia, being this disorder more frequent with the latter.

In this report we present a clinical case regarding an oxcarbazepine induced hyponatremia, and we hypothesized that oxcarbazepine could induce hyponatremia as a consequence of its influence on distal nephron where it could promote free water retention, urinary sodium loss, or both of them.

Besides, we proposed that a greater tubular sensitivity to oxcarbazepine than to carbamazepine could explain the different hyponatremia inducing capability between these two drugs

KEY WORDS: Oxcarbazepine. Hyponatremia. Physiopathology

RESUMEN

La carbamazepina y la oxcarbazepina son drogas antiepilépticas potencialmente inductoras de hiponatremia, siendo este disturbio más frecuente con ésta última.

En este reporte presentamos un caso de hiponatremia inducida por oxcarbazepina, y proponemos una potencial explicación fisiopatológica para esta entidad, a la cual se la considera consecuencia de un aumento a nivel de los túmulos colectores de la

reabsorción de agua libre, de la pérdida urinaria de sodio, o de ambos fenómenos combinados.

Además, postulamos que la mayor propensión a la aparición de hiponatremia con el uso de oxcarbazepina respecto del empleo de carbamazepina podría ser consecuencia de una mayor sensibilidad de los túmulos colectores a la primera de las drogas mencionadas.

PALABRAS CLAVE: Oxcarbazepina. Hiponatremia. Fisiopatología

INTRODUCTION

Hyponatremia is one of the most frequent electrolyte disorders associated to medication, being those drugs prescribed for psychological or neurological disorders the most dangerous ones in this sense¹.

Carbamazepine and oxcarbazepine are antiepileptic drugs which can induce hyponatremia, an adverse effect usually asymptomatic in the setting of these drugs^{2,3}.

Even though, both drugs are chemically related, since oxcarbazepine is a ketoderivative of carbamazepine, hyponatremia seems to be more associated to oxcarbazepine³⁻⁵. There is no explicative hypothesis for such difference in the literature⁶, then we present a case of oxcarbazepine induced hyponatremia, and potential explanation for its physiopathology in the present clinical report.

CASE REPORT:

Female patient, 71 years old, who had the following antecedents:

- Epilepsy under treatment with carbamazepine (600 mg/day)
- Hypertension treated with enalapril (10 mg/day) plus atenolol (25 mg/day)
- Pulmonary thromboembolism treated with warfarin (10 mg/day)

Since it was difficult to reach an adequate anticoagulation status in this patient, it was interpreted that the inductor enzymatic effect of carbamazepine could explain this refractory to anticoagulation. Then, it was decided to change the antiepileptic drug from carbamazepine (600 mg/day) to oxcarbazepine (600 mg/day) which has a lesser enzymatic induction effect.

Fourty eight hours after this change, the patient developed an asymptomatic hypotonic hyponatremia, with normal extracellular fluid, lowering her serum sodium level from 138 mmol/l progressively to 120 mmol/l.

Since, it was intended to keep the oxcarbazepine treatment, water restriction was effectively implemented (documented by a reduced fractional excretion of urea), but there was no amelioration in her serum sodium level (Table 1).

Table 1: laboratory values before and after water restriction

	Basal	After water restriction
Serum sodium (mmol/l)	120	122
Serum creatinine (mg/dl)	0.7	0.8
Serum urea (mg/dl)	33	47
Serum glucose (mg/dl)	110	100
FENa (%)	1.3	1.9
FEU (%)	63	55

FENa: fractional excretion of sodium. FEU: fractional excretion of urea

Then, enalapril, another potetial cause of hyponatremia, was discontinued and hypertension was controlled increasing her previous atenolol dose (25 mg/day to 50 mg/day). However, despite the above described therapeutical changes, her hyponatremia was not solved.

Finally, oxcarbazepine was stopped and carbamazepine was reintroduced as her antiepileptic treatment, while anticoagulation was handled using subcutaneous low weight heparin. Fourty eight hours after these changes serum sodium levels went back to

normal range.

DISCUSSION:

Although structurally related to carbamazepine, oxcarbazepine has several clinically relevant advantages over the former, including a more favorable pharmacokinetic profile and a better tolerability.

Because the metabolism of oxcarbazepine follows non-oxidative pathways, it has a lower propensity to induce hepatic oxidative enzymes and a reduced potential for drug-drug interactions. Additionally, oxcarbazepine does not undergo autoinduction^{3,7}.

Even though, early reports suggested that carbamazepine could induce excessive release of vasopressin and lead to inappropriate secretion of antidiuretic hormone, more recent studies have not found such hormonal increase⁸.

It was documented in another study that after a water load, serum sodium and free water clearance were diminished in persons (patients or volunteers) who were on oxcarbazepine. Besides, oxcarbazepine induced hyponatremia was not associated with significant elevation in serum vasopressin levels. These findings indicate that oxcarbazepine-induced hyponatremia is not attributable to the syndrome of inappropriate secretion of antidiuretic hormone⁷⁻⁸.

Moreover, it was also reported that serum natriuretic peptides levels were decreased in these hyponatremic patients⁷. Actually, in a study performed in patients on oxcarbazepine, serum aldosterone levels were increased in six normonatremic patients while these hormonal levels remained stable in 4 patients who were suffering from hyponatremia, suggesting that an increase in aldosterone levels could involve a compensatory mechanism to prevent hyponatremia in these patients³.

Besides, it is already known from Edelman equation ($\text{natremia} = \text{free water} / \text{sodium} + \text{potassium}$) that hypotonic hyponatremia can be basically a consequence of an increase in free water body content, sodium depletion or a combination of both mechanisms⁹.

Then, based on the above provided information, it could be hypothesized that the modification of collecting tubules induced by oxcarbazepine could lead them to an increased water reabsorption or/and sodium loss. Besides, a greater induction of these tubular changes in patients on oxcarbazepine respect to the carbamazepine induced ones, could explain the reported higher incidence of hyponatremia in patients on oxcarbazepine.

CONCLUSION:

Oxcarbazepine could induce hyponatremia as a consequence of its influence on distal nephron where it could promote free water retention, urinary sodium loss, or both of them.

A greater tubular sensitivity to oxcarbazepine influence respect to carbamazepine one could explain the different hyponatremia inducing capability between these two drugs.

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