

CARBAMAZEPINE AND OXCARBAZEPINE-INDUCED HYPONATREMIA IN PEOPLE WITH EPILEPSY

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ABSTRACT

Objective To ascertain possible determinants of carbamazepine (CBZ) and oxcarbazepine (OXC) induced hyponatremia in a large cohort of people with epilepsy.

Methods We collected data on serum sodium levels in people with epilepsy attending a tertiary epilepsy centre while on treatment with CBZ or OXC. We defined hyponatremia as $\text{Na}^+ \leq 134$ mEq/L and severe hyponatremia as $\text{Na}^+ \leq 128$ mEq/L.

Results We identified 1,782 people who had used CBZ (n=1,424) or OXC (n=358) of whom 50 were treated with both drugs. Data on sodium level measurements were available in 1,132 on CBZ and in 289 on OXC. Hyponatremia occurred in 26% of those taking CBZ and 46% taking OXC. This was severe in 7% in the CBZ group and 22% in the OXC group. Hyponatremia was symptomatic in 48% and lead to admissions in 3%. Age over 40 years, high serum levels of CBZ and OXC and concomitant use of other antiepileptic drugs were the main risk factors for hyponatremia in both treatment groups. Females on OXC were at a higher risk of hyponatremia than males. The risk of hyponatremia on CBZ was significantly associated with the risk of hyponatremia on OXC within a subgroup that used both drugs consecutively.

Significance Hyponatremia is a common problem in people taking CBZ or OXC. Regular ascertainment of sodium levels in those taking either drug is recommended and results should be acted upon.

Keywords: Antiepileptic drugs, sodium levels, adverse effects, electrolytes.

INTRODUCTION

The antiepileptic drugs (AEDs) carbamazepine (CBZ) and its keto-analogue oxcarbazepine (OXC) are among the drugs of choice for the treatment of focal epilepsy. The use of CBZ and OXC is limited by hyponatremia. It can lead to symptoms ranging from unsteadiness and mild confusion to seizures and coma although it is often assumed to be asymptomatic.^{1,2} Its severity depends on the absolute sodium levels and the rate of decline of sodium.³ The reported prevalence of CBZ and OXC induced hyponatremia (COIH) varies greatly; for CBZ the reported estimates are between 4 and 40% whilst for OXC they are between 23 and 73%.^{4,5} Data on risk factors for hyponatremia are limited. A few studies have looked at sex, age, dose and use of other AEDs, but results were inconclusive, often due to low sample size.

We aimed to confirm previous observations, evaluate the clinical characteristics of hyponatremic and identify possible determinants of COIH in a large cohort of people treated for epilepsy.

METHODS

An electronic database designed for pharmacogenomics studies (www.epipgx.eu), capturing all relevant clinical data with an emphasis on AED history, has been in use since 2010 at a tertiary referral centre for epilepsy (<http://www.sein.nl/en/>). It was used to identify all individuals who were prescribed CBZ or OXC and who had a recorded serum sodium level during therapy. Levels were measured during the course of routine monitoring. For each sodium level measurement, we recorded the date, serum level of CBZ or OXC and concomitant use of other AEDs. Most individuals had several measurements and we used the lowest sodium level recorded for each for the analysis. We defined hyponatremia as a sodium level ≤ 134 mEq/L, and severe hyponatremia as ≤ 128 mEq/L, in line with previous studies.^{5,6} Potentially predictive variables for hyponatremia tested were: CBZ/OXC serum levels, age, sex and concomitant AEDs. Clinical characteristics of those hyponatremic were retrieved from case notes. Symptoms present at the time of hyponatremia, which could not be explained by another clear cause such as overt AED intoxication or comorbidity were scored.

Statistics: Sodium levels were modelled either as a continuous variable or as a dichotomized variable (\leq or >134 mEq/L). Independent samples T-Tests for continuous variables and 2*2 tables with chi-squared tests for categorical variables were used to examine the association of the individual risk factors with hyponatremia. Linear regression was used to assess the relationship of these variables with sodium levels as a continuous variable in a multivariate analysis. The appropriateness of the multivariate linear regression was assessed by plotting standardised residuals, which were visually inspected for normality. Multivariate logistic regression was used to

assess the relationship of these variables with hyponatremia as a dichotomous variable.

In people with a sodium level ≤ 128 mEq/L information on co-medication other than AEDs was retrieved from case notes and differences in mean sodium levels between those using and not using these various medications were analysed with independent samples T-Tests.

In the subgroup analyses for users of both CBZ and OXC, means of sodium levels were compared with the paired samples T-Test and the McNemar test was used to analyze the differences for binary data, such as the occurrence of hyponatremia.

The statistical analysis was carried out on SPSS version 22.0 for Windows (SPSS Inc., Chicago, IL).

Ethics: The Ethical Committee of UMC Utrecht approved this investigation. All participants had previously provided written informed consent for data retrieval.

RESULTS

We identified 1,732 people (94% Caucasians) who had used CBZ (n=1,424) or OXC (n=358); sodium levels were not measured or not recorded in 361 (21%). Fifty people in the cohort had sodium levels measured during both CBZ and OXC treatment; no one used both drugs at the same time. Sodium levels were measured and recorded in 1,132 (79%) treated with CBZ (616 males) with a mean age of 41.8 ± 15.6 (years \pm SD) and a mean Na⁺ level of 138.4 ± 4.2 mEq/L. In the OXC group sodium levels were measured and recorded in 289 people (81%; 150 males), with a mean age of 37.2 ± 16.2 and a mean Na⁺ level of 135.7 ± 5.5 mEq/L. The average number of Na⁺ measurements was 1.71 ± 1.0 (min 1, max 11). Hyponatremia was seen in 26% (294/1,132) in the CBZ group and 46% (134/289) in the OXC group. Severe hyponatremia was found in 7% (81/1,132) in the CBZ group and in 22% (65/289) in the OXC group.

Hyponatremia was symptomatic in 48% (194/402, 26 missing data) of those found to have low sodium levels (35% in people with mild hyponatremia and 72% in severe hyponatremia). Among those symptomatic 6% had CBZ or OXC levels above the therapeutic range (10 with CBZ levels ≥ 11 , one with OXC level ≥ 35). Symptoms were mostly mild: dizziness (94/194; 48%), diplopia (48/194; 25%), unsteady gait (63/194; 32%), lethargy (37/194; 19%), cognitive slowness (26/194; 13%), tiredness (71/194; 37%), headache (30/194; 15%), nausea and vomiting (34/194; 18%). Falls were reported by 11% (21/194; 11%) and two who had severe hyponatremia sustained a fracture due to falling. In the group with severe hyponatremia seizure aggravation was seen in 22% (22/102). Six (3%, 5 with severe hyponatremia) were admitted to hospital for treatment.

CBZ/OXC and sodium levels (table 1)

Sodium levels were significantly associated with serum levels of CBZ ($p < 0.001$) and OXC ($p = 0.001$), but explained only a small part of the variance in the continuous sodium levels ($R^2 = 0.03$ and 0.04 , respectively, figure 1). Adjustment for age, sex and number of concomitantly used AEDs did not influence this association. All these cofactors were independently associated with continuous sodium levels. (suppl fig 1 for age and sodium levels) Mean sodium levels were lower in females (136.9 mEq/L with CBZ, 133.3 mEq/L with OXC) than in males (137.6 mEq/L with CBZ, 135.4 mEq/L with OXC) ($p = 0.012$ in CBZ and $p = 0.005$ in OXC).

CBZ/OXC and hyponatremia (table 2, table 3)

Serum levels of CBZ and OXC were significantly associated with hyponatremia, increasing the risk by a factor 1.20 (95% CI 1.12-1.28, $p < 0.001$) and 1.06 (95% CI 1.02-1.10, $p = 0.001$) per unit (mg/L) increase, respectively. This association remained significant in the multivariate logistic analysis.

When sodium levels were used as a dichotomized variable, sex remained a risk factor for hyponatremia in the OXC group, but not in the CBZ group. Women in the OXC group were more likely to develop hyponatremia (55%) than men (39%).

In those over 40 years hyponatremia was seen in 34% (compared with 17% <40 years) in the CBZ group and in 56% (compared with 39% <40 years) in the OXC group. In a multivariate logistic regression analysis, age over 40 increased the odds of hyponatremia by a factor 2.5 in the CBZ group and 2.2 in the OXC group.

The hyponatremia frequency in different age categories for CBZ and OXC users is shown in supplementary figure 2.

Monotherapy was associated with a lower risk of hyponatremia than polytherapy. After correction for drug levels, age and sex this association did not reach significance in the OXC group. The risk of hyponatremia was significantly increased with increasing number of concomitant AEDs in both groups.

Independent risk factors in both treatment groups were the concomitant use of clobazam (CLB) and phenytoin (PHT). Valproate (VPA) and phenobarbital (PB) were additional risk factors for hyponatremia in the CBZ group.

These observations were similar across sodium levels in three categories (≤ 128 , 129-134, ≥ 135) but numbers in the severe hyponatremia group were small (results not shown).

Severe hyponatremia and co-medication (table 4)

In those with a sodium level of ≤ 128 mEq/L (n=146) concomitant use of antidiabetics (n=5), NSAIDS (n=20), antipsychotics (n=15), antidepressants (n=10), antihypertensive drugs (n=25) (especially diuretics (n=4) and ACE inhibitors (n=8)) and proton pump inhibitors (n=16) was checked. In those treated with OXC, additional use of antihypertensive drugs and use of co-medication that, as a group, can influence sodium levels were significantly associated with a lower sodium level.

Users of CBZ and OXC (table 5)

Sodium levels were measured during CBZ and OXC treatment in 50 individuals who used the drugs sequentially (64% had CBZ first then had OXC). Mean sodium levels were significantly lower on OXC (131 mEq/L) when compared to CBZ treatment (135 mEq/L, $p<0.001$). Hyponatremia was seen more frequently than in the total cohort; during CBZ use in 40% (20/50) and during OXC use in 68% (34/50). The risk of hyponatremia on CBZ was significantly associated with the risk of hyponatremia on OXC within this group ($p=0.001$). Eighteen of the 20 who had hyponatremia on CBZ also developed hyponatremia on OXC. The remaining two were mildly hyponatremic (≥ 132 mEq/l).

DISCUSSION

CBZ and OXC are widely used but physicians should be aware of the high prevalence of COIH. We have seen a relatively high frequency of severe hyponatremia, especially in those treated with OXC. We checked potential co-medication that might also trigger hyponatremia. People who were on antihypertensives had a significantly lower mean sodium level in the OXC group. Only 3% (2/58) of this group used diuretics and 14% antihypertensives (including diuretics) compared with 24% use of diuretics in another study with a larger cohort of OXC treated people and a lower prevalence (11%) of severe hyponatremia.⁶ Co-medication does not seem to explain the higher prevalence of severe hyponatremia in the OXC group.

The rate of COIH was higher in the elderly and this was in line with previous reports.⁵ ⁷ The odds of hyponatremia were doubled in people over the age of 40 years. Thirst sensation, renal function, urine concentrating abilities and hormonal modulators of salt and water balance are often impaired in the elderly, which makes older people more susceptible to COIH.⁸ In a previous study⁵ a much stronger age effect was reported in the OXC treated group than in those treated with CBZ but the sample was smaller. We found that the age effect was comparable in both groups.

The subgroup analysis of those who used CBZ and subsequently OXC suggests that an individual with hyponatremia associated with CBZ is also likely to develop hyponatremia while taking OXC. In an individual who does not develop hyponatremia with CBZ, there is a 53% chance of hyponatremia if subsequently OXC is used. The underlying mechanisms are likely to be similar but seem apparently more efficient

when OXC is used. This analysis also implies that a subset of people may be genetically predisposed to COIH.

Our findings suggest that women seem to be at higher risk of developing hyponatremia if taking OXC. In the CBZ group being female was a risk factor in the linear regression analysis, but with a very small effect size. COIH is probably caused by antidiuresis where CBZ and OXC are thought to stimulate the vasopressin water reabsorption pathway.⁹ The *AVPR2* gene, coding for the vasopressin 2 receptor (V2R) which plays a key role in water reabsorption, is located on the X chromosome in a region (Xq28) with high probability of escape from inactivation.¹⁰ Escape from inactivation results in higher expression of levels of transcript in females.^{11,12} This provides a possible explanation for why women are at a higher risk of hyponatremia, especially with the use of drugs that stimulate V2R. The underlying mechanisms seem to be more susceptible to OXC possibly through a stronger effect of OXC, compared with CBZ, on V2R. The use of OXC could therefore have a larger influence in women.

In a larger cohort study on OXC induced hyponatremia a sex difference was not found but within this cohort the mean age was 15 years higher than the mean age in our OXC cohort.⁶ The effect of impaired renal function at older age on the COIH risk was stronger in this study than the effect of sex difference. So in an older cohort this sex effect could be missed. Perhaps also the difference in ethnic background plays a role. Previous studies reported conflicting results regarding the association between CBZ and OXC dose and hyponatremia. Some smaller studies did find a dose response relationship,¹³⁻¹⁶ but larger studies could not confirm this.^{5,6} We found a significant relationship between CBZ and OXC drug levels and hyponatremia, but the effect size was small. This might explain why this was not seen in some other

studies. Staying below the 'mean relatively safe drug level' (7.4 mg/L for CBZ and 18.7 mg/L for OXC) might lower the need to withdraw these drugs due to hyponatremia.

We found that concomitant use of CLB and PHT in both groups and VPA and PB in the CBZ group may increase the risk of hyponatremia. The diuretic response to a water load was previously tested and found to be significantly greater in those taking carbamazepine and phenytoin in combination than in those on carbamazepine monotherapy¹⁷; this may explain our finding. Concomitant use of VPA and PB were also previously described as risk factors for CBZ induced hyponatremia.⁷ A previous study suggested OXC in combination with levetiracetam (LEV) was a risk factor⁵, but we found that concomitant use of LEV did not influence hyponatremia risk in either group.

One limitation of this study is that there were no recorded sodium levels for a fifth of the cohort. This, however, may reflect clinical practice in which some people, due to pressure of time and dislike of venipuncture, do not have samples taken for assay. The study was conducted at a single tertiary referral centre and it is likely that levels were estimated more frequently than in the primary or secondary levels of care.

It is important for clinicians to be aware of the high prevalence of COIH and nonspecific symptoms. Mild to moderate COIH may cause lethargy, cognitive slowness, headache, dizziness and nausea. Severe COIH may lead to falls, seizure aggravation and hospitalization.^{6,9} We found mild symptoms in almost half of those with hyponatremia although due to the design we used we can't be certain if these symptoms were due to hyponatremia or if another cause, such as high AED levels could be playing a role. Of interest, is that only 6% of the symptomatic had high

levels of either CBZ or OXC at the time. We have not systematically collected data on levels of other concomitant AEDs or of metabolites of CBZ and OXC.

A recent population-based study found that CBZ use compared to no antiepileptic use was associated with a 8.2 higher relative risk of hospitalization with hyponatremia within 30 days of drug initiation in people over 65 years.¹⁸ To prevent this, physicians should have a low threshold of suspicion for this common adverse effect and checking sodium levels should be routine in clinical practice for people taking either of these drugs. Mild hyponatremia can be treated with fluid restriction; in case of severe hyponatremia we would recommend the introduction of an alternative antiepileptic drug with the gradual withdrawal of either CBZ or OXC. Alternative antiepileptic medication also needs to be considered especially in the elderly, females and in those on multiple AEDs, before hyponatremia develops. Prospective studies are warranted to establish the true frequency of symptomatic hyponatremia.

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Author Disclosures

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Author Contributions

BB, JWS, and BK conceptualised and designed the study. BB collected the data. BB and JvdP carried out the statistical analyses. BB drafted the manuscript. JvdP, GJdH, JWS, DL and BK critically revised the manuscript. All approved the final version. BK and JWS are the guarantors.

Supplemental Data: STROBE Statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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FIGURE LEGENDS

Fig 1.

Sodium levels in relation to drug levels and age

Relationship between sodium level (Na^+ mEq/L) and drug level (mg/L) and relationship between sodium level and age (years) within both the carbamazepine (CBZ) and oxcarbazepine (OXC) treatment group.

SUPPLEMENTARY FIGURE LEGENDS

Suppl. fig 1.

Mean sodium levels in different age categories for carbamazepine and oxcarbazepine users.

Suppl. fig 2.

Hyponatremia frequency in different age categories for carbamazepine and oxcarbazepine users.

TABLES

Table 1. Univariate and multivariate analysis of demographic and clinical data with sodium level (mEq/l) as dependent variable.

	Univariate Analysis								Multivariate Analysis			
	carbamazepine				oxcarbazepine				carbamazepine		oxcarbazepine	
	N	R ²	Regr. coeff	P-value	N	R ²	Regr. coeff	P-value	Regr. coeff	P-value	Regr. coeff	P-value
drug level (mg/L)	1,008	0.025	-0.34	<0.001	257	0.039	-0.17	0.001	-0.31	<0.001	-0.19	<0.001
age (years)	1,132	0.078	-0.09	<0.001	289	0.040	-0.08	0.001	-0.08	<0.001	-0.06	0.007
sex*	1,132	0.006	0.76	0.010	289	0.027	2.11	0.005	0.91	0.002	2.30	0.003
NcoAEDs	1,087	0.018	-0.77	<0.001	277	0.054	-1.81	<0.001	-0.64	<0.001	-1.32	0.005
									n=968	R ² =0.116	n=245	R ² =0.135

Regr. coeff= regression coefficient.

NcoAED= number of concomitant AEDs used. * reference group= female

Table 2. Univariate analyses of demographic and clinical data with hyponatremia ($\text{Na} \leq 134 \text{ mEq/L}$) as dependent variable.

		carbamazepine			oxcarbazepine		
		na< =134	na>134	p-value	na< =134	na>134	p-value
mean drug level							
(mg/L)		8.3	7.4	<0.001	21.7	18.7	0.001
mean age (yrs)		49.1	39.3	<0.001	40.6	34.3	0.001
AgeCat40	≤ 40	88 (17%)	440 (83%)	<0.001	64 (39%)	101 (61%)	0.003
	>40	206 (34%)	398 (66%)		70 (56%)	54 (44%)	
sex	m	152 (25%)	464 (75%)	0.28	58 (39%)	92 (61%)	0.006
	f	142 (28%)	374 (72%)		76 (55%)	63 (45%)	
monotherapy	yes	53 (17%)	260 (83%)	<0.001	29 (36%)	52 (64%)	0.03
	no	230 (30%)	544 (70%)		99 (51%)	97 (49%)	
CLB	yes	56 (42%)	80 (59%)	<0.001	31 (70%)	13 (30%)	<0.001
	no	227 (24%)	724 (76%)		97 (42%)	136 (58%)	
PHT	yes	34 (38%)	56 (62%)	0.008	17 (77%)	5 (23%)	0.002
	no	249 (25%)	748 (75%)		111 (44%)	144 (56%)	
VPA	yes	90 (31%)	197 (69%)	0.02	28 (44%)	35 (56%)	0.73
	no	193 (24%)	607 (76%)		106 (47%)	120 (53%)	
PB	yes	22(38%)	36(62%)	0.03	5 (71%)	2 (29%)	0.18
	no	261(25%)	768(75%)		129 (46%)	153 (54%)	

AgeCat40 = age category split at 40 years; CLB=clobazam, PHT= phenytoin, VPA= valproic acid, PB= phenobarbital,

Table 3. Multivariate logistic regression analysis of demographic and clinical data with hyponatremia as dependent variable

	carbamazepine (n=968)				oxcarbazepine (n=245)			
	Odds	95% C.I.		<i>P</i> -value	Odds	95% C.I.		<i>P</i> -value
	Ratio	Lower	Upper		Ratio	Lower	Upper	
drug level (mg/L)	1.23	1.14	1.315	<0.001	1.08	1.04	1.12	<0.001
age (years)	1.04	1.03	1.05	<0.001	1.03	1.01	1.04	0.004
sex*	1.29	0.95	1.76	0.11	2.25	1.29	3.93	0.004
NcoAEDs	1.45	1.22	1.73	<0.001	1.98	1.13	2.26	0.008
AgeCat>40^a	2.51	1.83	3.45	<0.001	2.24	1.28	3.90	0.004
monotherapy^b	0.43	0.30	0.62	<0.001	0.64	0.35	1.16	0.14
VPA^b	1.82	1.29	2.58	0.001	1.20	0.64	2.27	0.57
PB^b	1.98	1.075	3.66	0.03	3.27	0.53	20.18	0.20
CLB^b	2.41	1.57	3.68	<0.001	3.84	1.75	8.41	0.001
PHT^b	2.40	1.43	4.01	0.001	6.30	2.04	19.43	0.001

NcoAEDs = number of concomitant antiepileptic drugs; AgeCat>40 =age category above 40 years;

* reference group= male

a Model with covariates: drug level, sex and NCoMed

b Each therapy is separately tested in a model with covariates: drug level, age and sex

Levetiracetam, lamotrigine, lacosamide, topiramate, gabapentin, clonazepam, vigabatrin and ethosuximide were not significantly associated with hyponatremia in a multivariate analysis.

Table 4. The effect of non-AED co-medication in severe CBZ and OXC induced hyponatremia ($\text{Na} \leq 128 \text{ mEq/L}$).

Comedication		carbamazepine			oxcarbazepine		
		mean Na^+	N^a	<i>P</i> -value	mean Na^+	N^a	<i>P</i> -value
Antihypertensive drugs	no	125.13	56	0.29	125.69	52	0.001
	yes	126.00	17		121.88	8	
Diuretics	no	125.35	71	0.69	125.34	58	0.03
	yes	124.50	2		120.50	2	
ACE inhibitors	no	125.22	67	0.32	125.34	58	0.03
	yes	126.50	6		120.50	2	
No comedication	no	125.42	33	0.81	124.21	24	0.04
	yes	125.25	40		125.83	36	

a No data on co-medication was available for 13 people.

Table 5. Hyponatremia in subgroup using both carbamazepine and oxcarbazepine sequentially.

			Oxcarbazepine		Total
			Na≤134	Na>134	
Carbamazepine	Na≤134	N	18	2	20
	% within Na≤134		90,0%	10,0%	
	Na>134	N	16	14	30
	% within Na≤134		53,3%	46,7%	
Total			34	16	50

McNemar test: p= 0.001

Key points

- Hyponatremia was seen in a quarter of those taking carbamazepine (CBZ) and in almost half on oxcarbazepine (OXC).
- Age over 40 years, high levels of CBZ and OXC and concomitant use of other antiepileptic drugs were risk factors for CBZ and OXC induced hyponatremia.
- Females on OXC were at a higher risk of hyponatremia than males.
- The risk of hyponatremia on CBZ was significantly associated with the risk of hyponatremia on OXC within a subgroup that used both drugs subsequently.
- Regular sodium level assays in those taking CBZ or OXC are recommended and results should be acted upon.