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Differences in associations of antiepileptic drugs and hospitalization due to hyponatremia: A population–based case–control study

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ABSTRACT

Purpose: Hyponatremia induced by antiepileptic drugs is common, but detailed evidence is lacking. This can be problematic for the treating neurologist confronted with a patient with severe hyponatremia in need of an alternative drug. The objective of this study was to examine the association between individual antiepileptic drugs and hospitalization due to hyponatremia.
Methods: This was a register-based case–control study of patients in the general Swedish population. We included 14,359 individuals with a principal diagnosis of hyponatremia and 57,383 matched controls. The association between newly initiated (≤90 days) and ongoing antiepileptic treatment was investigated using multivariable logistic regression adjusting for concomitant drugs, medical conditions, previous hospitalizations and sociaoeconomic factors.
Results: For newly initiated antiepileptic drugs, adjusted ORs (95% CI) for hospitalization due to hyponatremia, compared to controls, were: carbamazepine 9.63 (6.18–15.33); phenytoin 4.83 (1.14–25.76); valproate 4.96 (2.44–10.66); lamotrigine 1.67 (0.70–4.08); levetiracetam 9.76 (4.02–27.59) and gabapentin 1.61 (1.08–2.38). Newly initiated oxcarbazepine treatment was only found in the hyponatremia group and not in controls. Adjusted ORs (CI) for individuals with ongoing treatment ranged from 7.97 (3.70–18.50) for oxcarbazepine to 0.83 (0.64–1.06) for gabapentin.
Conclusion: There was a strong association between newly initiated treatment with carbamazepine, oxcarbazepine and levetiracetam, and hospitalization due to hyponatremia. The corresponding association for phenytoin and valproate was moderate. The risk for hyponatremia was lower during ongoing treatment. Lamotrigine and gabapentin had the lowest risk both during initiation and ongoing treatment and may be advantageous in patients at risk of developing hyponatremia.

1. Introduction

The most frequent electrolyte disorder in hospitalized patients is hyponatremia [1]. The clinical spectrum in hyponatremia ranges from mild, non-specific symptoms such as fatigue, headache, and gait instability to life-threatening symptoms such as seizures, coma and ultimately death, secondary to brain oedema [2,3]. Pharmaceutical drugs, e.g., thiazide diuretics, antidepressants and antiepileptic drugs are common causes of both asymptomatic and symptomatic hyponatremia [4]. Since epilepsy is a common disease requiring long-term treatment with antiepileptic drugs, adverse effects such as hyponatremia can be a major problem and deaths have been described [5]. Most studies on antiepileptic drugs have been small and focused on the effect on sodium levels without addressing the clinical consequences, such as hospitalization [6,7]. This lack of evidence can be problematic for the treating neurologist, for example when confronted with a patient with severe hyponatremia, in need of an alternative drug. The aim of this study was to investigate the association between individual antiepileptic drugs and the risk of hospitalization due to hyponatremia.

2. Methods

2.1. Study design and setting

This was a retrospective Swedish population–based case–control study.

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2.2. Participants

In a hospitalized patient, the principal diagnosis reflects the condition that best motivates the admission. The attending physician in Sweden codes all admissions and specialist outpatient visits with *International Classification of Diseases* codes, 10th Revision (ICD10) [8]. All hospitalized patients 18 years or older, with a first-ever (defined as not occurring since 1 January 1997) principal ICD10 code of E87.1 (hyponatremia) or E22.2 (syndrome of inappropriate ADH secretion [SIADH]) in The National Patient Register (NPR) (see below) between 1 October 2005 and 31 December 2014 were defined as cases. Controls matched for age, sex and municipality (4 controls per case) who had not been diagnosed with hyponatremia since 1 January 1997 were selected from the Total Population Register. The study population in the present study has been described in detail in a recent publication [9].

2.3. Variables

In Table 1, all variables included in the multiple logistic regression analysis are shown, along with their definitions. Antiepileptic drugs included in the analysis were: carbamazepine, oxcarbazepine, phenytoin, valproate, lamotrigine, levetiracetam, and gabapentin. ICD10 codes, Anatomical Therapeutic Chemical (ATC) codes, and parameters from the Longitudinal integration database for health insurance and labor market studies (LISA)-register were used to define potential confounders. A documented dispensing within 90 days prior to the index date was used to define antiepileptic drug exposure. Almost all patients in Sweden

Table 1
Variables included in the multiple logistic regression analysis and their definition.

Variables	Codes
Antiepileptic drugs	**ATC codes beginning with**
Carbamazepine	N03AF01
Oxcarbazepine	N03AF02
Phenytoin	N03AB02
Valproate	N03AG01
Lamotrigine	N03AX09
Levetiracetam	N03AX14
Gabapentin	N03AX12
Other drugs	
Furosemide	C03C
Thiazides	C03A, C09BA, C09DA
Fluoroquinolones	J01MA
Macrolides	J01FA
Trimethoprim sulfamethoxazole	J01EE
Citalopram	N06AB04
Escitalopram	N06AB10
Sertraline	N06AB06
Other SSRIs[a]	N06AB03, N06AB05, N06AB08
Tricyclic antidepressants	N06AA
Mirtazapine	N06AX11
Venlafaxine	N06AX16
Other antidepressants	N06AX03, N06AX12, N06AX18, N06AX21, N06AX22, N06AX26, N06AG02
Proton pump inhibitors	A02BC
Amiodarone	C01BD01
Tramadol	N02AX02
Diseases	**ICD10 codes beginning with**
Renal diseases	N17-19, procedure codes DR016, DR024, KAS00, KAS10, KAS20
Sepsis	A41
Pneumonia	J18
Meningitis	G00-G07
Ischemic heart disease	I20-25
Malignant disease	C
Congestive heart failure	I50
Pancreatic disease	K85, K860-1
Inflammatory bowel disease	K50-K51
Liver diseases	K70-77 Procedure codes JJB, JJC
Cerebrovascular diseases	I60-64, I69
Hypothyroidism	E03, E06.3
Malnutrition	E43.9, E41.9
Chronic obstructive pulmonary disease	J44
Pulmonary embolism	I26
	Combination of ATC- and ICD-10 codes, each beginning with
Alcoholism	**ATC:** N07BB03, N07BB04, N07BB01, N07BB05, N07BB
	ICD10: E244, F10, G312, G621, G721, I426, K292, K70, K860, O354, P043, Q860, T51, Y90-91, Z502, Z714
Adrenal insufficiency	**ATC:** N07BB03, N07BB04, N07BB01, N07BB05, N07BB
	ICD10: E27, K70.3, K70.4, K70.1
Diabetes	**ATC:** A10A, A10AB
	ICD10: E10-E14
Other factors	
Education	Increasing levels of education from 1–6, continuous variable
Income	Income in Swedish crowns during 1 year, continuous variable
Unemployment	Number of days, continuous variable
Drug use	Number of dispensed drugs 90 days prior to index date, categorised into <4, 4–7, 8–12 and >12 drugs
Previous hospitalization	>2 days within 2 years prior to index date

[a] Selective serotonin reuptake inhibitors.