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Original Article

Tramadol- and codeine-induced severe hyponatremia: A Swedish population-based case-control study

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ABSTRACT

Background: Although tramadol and codeine occasionally have been reported to cause hyponatremia the evidence is scarce. The objective of this investigation was to study the association between weak opioids (tramadol and codeine) and hospitalization due to hyponatremia.

Methods: This was a register-based case-control study of the general Swedish population. Those hospitalized with a principal diagnosis of hyponatremia (n = 14,359) were compared with matched controls (n = 57,383). Multivariable logistic regression adjusting for co-medication, diseases, previous hospitalizations and socioeconomic factors was used to explore the association between severe hyponatremia and the use of tramadol or codeine. Furthermore, newly initiated (≤90 days) and ongoing use was investigated separately.

Results: Compared to controls, the unadjusted OR (95%CI) for hospitalization due to hyponatremia was 2.45 (2.26–2.66) for tramadol and 3.19 (2.92–3.47) for codeine. However, after adjustment for confounding factors the risk decreased (adjusted OR: 1.17 [1.08–1.26] and 1.14 [1.03–1.26], respectively). Newly initiated treatment with tramadol or codeine showed a significant association (adjusted OR 2.34 [95%CI 2.01–2.72] and 2.20 [95%CI 1.87–2.60], respectively). In contrast, for ongoing therapy the corresponding adjusted ORs were not elevated (adjusted OR: 0.70 [95%CI 0.61–0.80] and 1.14 [95%CI 0.99–1.30, respectively).

Conclusions: Associations were found between tramadol or codeine usage and hospitalization due to hyponatremia which were markedly increased in those newly initiated. The risk associated with long-term use was not increased. The association may be causally related to the drugs, although an effect due to pain, nausea or the underlying disease cannot be excluded.

1. Background

In hospitalized patients different electrolyte disturbances are frequent, with up to 30% of all admitted patients affected by hyponatremia [1,2]. Hyponatremia can cause mild, non-specific symptoms such as lethargy, agitation and confusion but also severe life-threatening symptoms such as seizures, coma and death due to brain oedema [3–6]. Hyponatremia is often defined according to the severity of the serum sodium concentration: mild hyponatremia being a concentration between130 and 135 mmol/L, moderate hyponatremia between 125 and 129 mmol/L and severe (profound) hyponatremia < 125 mmol/L [6]. However, the definition of hyponatremia can also be based on symptoms where moderate or severe symptomatic hyponatremia, respectively, are any biochemical degree of hyponatraemia in the presence of moderately severe or severe symptoms of hyponatraemia [6]. A common cause of hyponatremia requiring hospitalization is drugs such as thiazide diuretics, antidepressants, antiepileptic drugs and antipsychotics [7–12].

Tramadol is a widely used, weak centrally acting synthetic opioid analgesic with monoaminergic actions similar to serotonin-norepinephrine reuptake inhibitors (SNRIs) [13]. Codeine, similarly used for the treatment of mild to moderate pain, is a prodrug for which the pharmacological effect is dependent on *O*-demethylation to morphine. Occasional case reports have indicated that tramadol [14–18] as well as codeine [19] may cause hyponatremia. The mechanism for tramadol as well as codeine-induced hyponatremia is believed to be the syndrome of

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inappropriate ADH-secretion (SIADH). For tramadol, an additional plausible mechanism may be the inhibition of the reuptake of noradrenaline and serotonin increasing the risk of SIADH in analogy with the risk associated with SSRIs and SNRIs treatment [7–10]. In fact, in a recent population-based study, the use of tramadol was associated with an increased risk of hospitalization due to hyponatremia compared to codeine within the first 30 days of use, suggesting that codeine may be preferable in patients prone to develop hyponatremia [20]. However, the evidence remains insufficient.

The aim of this study was to investigate the association between treatment with tramadol or codeine and hospitalization due to hyponatremia. Furthermore, we aimed to separate newly initiated and ongoing use to study if there was any temporal association.

2. Methods

This retrospective case–control study used the Swedish general population. In order to capture the main cause of the admission, the principal diagnosis of each patient was used. All hospitalizations and outpatient visits are coded by the attending physicians in Sweden using the *International Classification of Diseases* codes, 10th Revision (ICD10) [21]. Cases were all adult patients (≥18 years) hospitalized 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) (vide infra) during the period 1 October 2005 to 31 December 2014. Pseudohyponatremia should not be diagnosed with one of these ICD10 codes as a principal diagnosis but with the diagnosis of the cause of pseudohyponatremia, e.g., multiple myeloma and other monoclonal gammopathies. For each case, four age-, sex- and municipality-matched controls with no previous diagnosis of hyponatremia (since 1 January 1997) were randomly identified from the Total Population Register. More details on this process can be found elsewhere [10–12,22].

In Table 1, all variables used in the multiple logistic regression analysis are presented. In order to identify potential confounders for hyponatremia, ICD10 codes, Anatomical Therapeutic Chemical (ATC) codes, and parameters from the Longitudinal integration database for health insurance and labor market studies (LISA)-register were utilized [10]. Exposure to tramadol or codeine (excluding formulations for cough or diarrhea) was defined as a documented dispensation within 90 days prior to the index date, i.e., the date of hospitalization due to hyponatremia. In the matched controls, the index date was the hospitalization date of their case. For ongoing treatment, almost all drugs are dispensed every 90 days in Sweden [10]. Almost all patients on tramadol used 50 mg tablets (81.6%) and those on codeine 60 mg tablets (96.8%). However, the number of tablets used per day was not available. Concurrent disorders were controlled for since 1 January 1997 to the index date. The only exception being infectious diseases, which were controlled for within 90 days before the index date (Table 1). Newly initiated tramadol or codeine use was defined as treatment introduced within 90 days before the index date and at least 12 months of no exposure prior to that. The definition of ongoing tramadol or codeine use also required one or more dispensations in the period 91 to 454 days prior to the index date.

The Swedish personal identification number was used for linkage between the population-based registers. The three registers used were NPR, The Swedish Prescribed Drug Register (SPDR) and the LISA-register [21,23,24]. The NPR contains all the admission diagnoses since 1997 in Sweden using ICD10 codes, while the SPDR contains all prescriptions dispensed in Sweden since 1 July 2005. To adjust for socioeconomic variables, the LISA register was employed. The Regional Ethical Review Board in Stockholm approved the study.

2.1. Statistical analysis

The associations between hospitalization due to hyponatremia and

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

Variables	Codes
	ATC codes beginning with
Drugs of primary interest	
Tramadol	N02AX02
Codeine	R05DA04, N02AA59, N02AJ06, N02AJ07, N02AJ08, N02AJ09, N02BE51
Antiepileptic drugs	
Carbamazepine	N03AF01
Oxcarbazepine	N03AF02
Phenytoin	N03AB02
Valproate	N03AG01
Lamotrigine	N03AX09
Levetiracetam	N03AX14
Gabapentin	N03AX12
Diuretics and drugs on the renin-angiotensin system	
Furosemide	C03C
Thiazides	C03A, C09BA, C09DA, C03EA
Agents acting on the renin-angiotensin system	C09
Antibiotics	
Fluoroquinolones	J01MA
Macrolides	J01FA
Trimethoprim sulfamethoxazole	J01EE
Antidepressants	
SSRIs	N06AB
Tricyclic antidepressants	N06AA
Other antidepressants	N06AX
Other drugs	
Amiodarone	C01BD01
Desmopressin	H01BA02
Proton pump inhibitors	A02BC, A02BD06
Antipsychotics (including lithium)	N05A
NSAIDs	M01AA, M01AB, M01AC, M01AE, M01AG, M01AH, M01AX01, N02AJ08, N02AJ19
	ICD10 codes beginning with
Renal diseases	
Renal insufficiency	N17-19, procedure codes DR016, DR024, KAS00, KAS10, KAS20
Infections	
Sepsis	A41
Pneumonia	J18
Meningitis	G00–G07
Heart and vascular diseases	
Ischemic heart disease	I20-25
Congestive heart failure	I50
Cerebrovascular diseases	I60-64, I69
Gastrointestinal diseases	
Pancreatic disease	K85, K860-1
Inflammatory bowel disease	K50-51
Liver diseases	K70-77 Procedure codes JJB, JJC
Other diseases	
Hypothyroidism	E03, E06.3
Malnutrition	E43.9, E41.9
COPD	J44
Pulmonary embolism	I26
Malignancy	C
	Combination of ATC- and ICD10 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: H02AA, H01BA ICD10: E27.1, E27.2, E27.3, E27.4, E25
Diabetes mellitus	ATC: A10 ICD10: E10-E14
Socioeconomic factors	
Education	Increasing levels of education from 1 to 6, continuous variable

(*continued on next page*)

Table 1 (*continued*)

Variables	Codes
Income	Income in Swedish crowns during 1 year, continuous variable
Unemployment	Number of days, continuous variable
Proxy for frailty	
Drug use	Number of dispensed drugs 90 days prior to index date, categorised into < 4, 4–7, 8–12 and > 12 drugs
Duration of hospitalization	≥ 3 days

SSRIs, selective serotonin reuptake inhibitors. NSAIDs, non-steroidal anti-inflammatory drugs. COPD, chronic obstructive pulmonary disease.

tramadol or codeine were analyzed by means of univariable and multivariable logistic regression. In these models, the reference group was defined as individuals unexposed to any of the drugs or variables adjusted for (see Table 1). The associations between tramadol or codeine and hospitalization requiring hyponatremia in cases and controls were reported as unadjusted and adjusted (for potential confounders) odds ratios (OR), with 95% confidence intervals (95%CI). *P*-values < .05 were considered statistically significant. For all analyses R version 3.3.2 was used [25].

3. Results

A principal discharge diagnosis of hyponatremia was recorded in 14,359 adult individuals. From the Total Population Register 57,382 matched controls were identified. The majority (72%) were female and the median age was 76 years (range 18–103). Table 2 presents a selection of medical conditions and use of tramadol and codeine at baseline (index date), stratified by age. The most frequent medical disorders were hypertension, malignancy, ischemic heart disease, diabetes and alcoholism. In total, 6.9% of the cases had recently been dispensed tramadol compared to only 2.9% of the controls. For codeine the dispension were 6.5% and 2.2%, respectively.

The association between exposure to tramadol or codeine and hospitalization due to hyponatremia is presented in Fig. 1. Compared to controls, the unadjusted OR (95%CI) for hospitalization due to hyponatremia was 2.45 (2.26–2.66) for tramadol and 3.19 (2.92–3.47) for codeine. However, after adjustment for confounding factors the risk decreased (adjusted OR: 1.17 [1.08–1.26] and 1.14 [1.03–1.26], respectively).

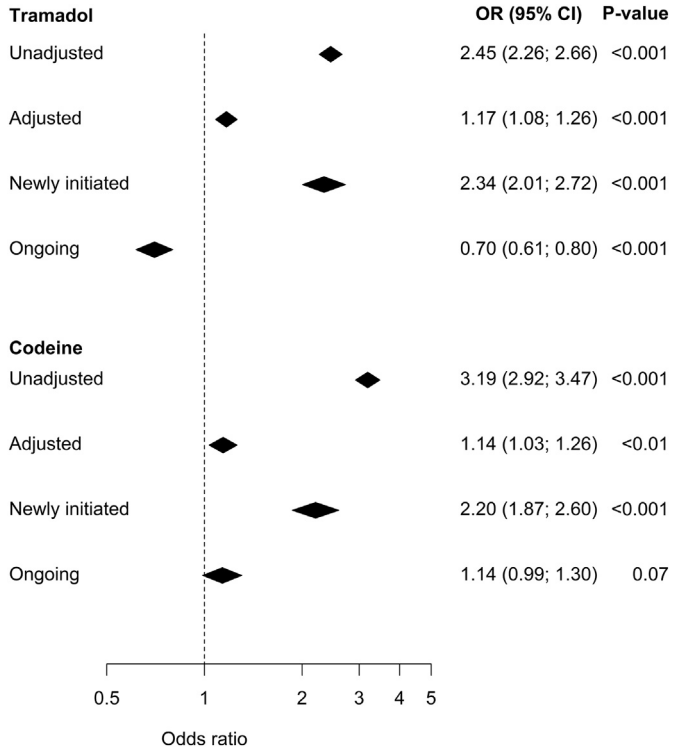

Fig. 1. The unadjusted and adjusted (adjusted for all the confounding factors in Table 1) odds ratios (ORs), including 95% confidence intervals (95% CI) for hospitalization due to hyponatremia in patients on tramadol and codeine. The newly initiated (< 90 days) and ongoing treatment are all adjusted ORs (95% CI).

As also illustrated in Fig. 1, we also analyzed the effect of newly initiated tramadol and codeine use versus ongoing therapy (adjusted

Table 2
Medical characteristics (selection of items from Table 1), age stratified, in addition to tramadol and codeine use among cases (hospitalized with a principal diagnosis of hyponatremia) and controls at index date.

	Cases (*n* = 14,359)			Controls (*n* = 57,382)		
	18–64 years (*n* = 3421)	65–79 years (*n* = 4979)	80- years (*n* = 5959)	18–64 years (*n* = 13,684)	65–79 years (*n* = 19,916)	80- years (*n* = 23,782)
Diagnosis						
Hypertension	1308 (38.2%)	3195 (64.2%)	4315 (72.4%)	1163 (8.5%)	5028 (25.2%)	9145 (38.5%)
Malignancy	595 (17.4%)	1401 (28.1%)	1830 (30.7%)	1144 (8.4%)	3919 (19.7%)	6188 (26%)
Ischemic heart disease	272 (8.0%)	1007 (20.2%)	1529 (25.7%)	469 (3.4%)	2399 (12%)	5012 (21.1%)
Diabetes mellitus	592 (17.3%)	1016 (20.4%)	815 (13.7%)	767 (5.6%)	2539 (12.7%)	3275 (13.8%)
Alcoholism	1301 (38%)	880 (17.7%)	104 (1.7%)	462 (3.4%)	443 (2.2%)	123 (0.5%)
Congestive heart failure	226 (6.6%)	620 (12.5%)	1054 (17.7%)	105 (0.8%)	889 (4.5%)	3499 (14.7%)
Cerebrovascular diseases	319 (9.3%)	659 (13.2%)	906 (15.2%)	202 (1.5%)	1190 (6.0%)	3148 (13.2%)
COPD	345 (10.1%)	714 (14.3%)	418 (7.0%)	132 (1.0%)	773 (3.9%)	1053 (4.4%)
Adrenal insufficiency	162 (4.7%)	189 (3.8%)	235 (3.9%)	37 (0.3%)	105 (0.5%)	198 (0.8%)
Renal diseases	185 (5.4%)	252 (5.1%)	194 (3.3%)	73 (0.5%)	287 (1.4%)	738 (3.1%)
Liver diseases	254 (7.4%)	237 (4.8%)	62 (1.0%)	113 (0.8%)	167 (0.8%)	137 (0.6%)
Pancreatic diseases	136 (4.0%)	113 (2.3%)	78 (1.3%)	74 (0.5%)	158 (0.8%)	281 (1.2%)
Drugs of interest, total						
Tramadol	239 (7.0%)	387 (7.8%)	362 (6.1%)	292 (2.1%)	577 (2.9%)	811 (3.4%)
Codeine	266 (7.8%)	353 (7.1%)	325 (5.5%)	227 (1.7%)	430 (2.2%)	583 (2.5%)
Drug of interest, newly initiated treatment						
Tramadol	95 (2.8%)	186 (3.7%)	214 (3.6%)	77 (0.6%)	173 (0.9%)	230 (1.0%)
Codeine	80 (2.3%)	145 (2.9%)	177 (3.0%)	78 (0.6%)	136 (0.7%)	208 (0.9%)

COPD, chronic obstructive pulmonary disease.

ORs). Newly initiated treatment with tramadol and codeine showed a significant association with hospitalization for hyponatremia (adjusted OR: 2.34 [2.01–2.72] and 2.20 [1.87–2.60], respectively). In contrast, in patients treated > 90 days, the adjusted ORs revealed a lower risk for hyponatremia among tramadol-treated subjects and a non-significant increased risk among codeine-treated subjects (adjusted OR 0.70 [0.61–0.80] and 1.14 [0.99–1.30], respectively).

4. Discussion

This is the first population-based case-control study reporting on the risk of tramadol and codeine-related hyponatremia in a cohort of patients hospitalized due to hyponatremia. The associations with hyponatremia requiring hospitalization were similar for tramadol and codeine (adjusted OR 1.17 and 1.14, respectively), with similar markedly increased risk for newly initiated treatment (adjusted OR 2.34 and 2.20, respectively). In contrast, ongoing therapy was not associated with an increased risk.

The mechanism of tramadol and codeine-induced hyponatremia is believed to be SIADH [15–20], which is the most common cause of drug-induced hyponatremia [7]. Morphine has been shown to result in high ADH levels indicating central opioid receptor mediated stimulation of ADH fibers [26], and hospital-acquired hyponatraemia [27]. However, other studies, both animal and human, have found that opioids can both simulate and inhibit ADH [28]. The inconsistencies may be a result of the fluid status and/or the adverse effects of the individual opioid [28]. For tramadol, another plausible mechanism may be the inhibition of the reuptake of noradrenaline and serotonin [13], increasing the risk of SIADH, analogous with the risk associated with SSRIs and SNRIs treatment [7,10]. In accordance with our previous findings on some other drug classes [10,11,22], we could demonstrate a clear temporal association between initiation of tramadol or codeine and hospitalization due to hyponatremia. Also in the limited previous literature on tramadol- and codeine-induced hyponatremia, the hyponatremia event seemed to have occurred soon after initiation of the drug which may point towards a pharmacologic underlying association [14–20]. Hyponatremia is increasingly prevalent with higher age [29], which to an extent can be explained by the more frequent *co*-morbidities and polypharmacy known to increase the risk for hyponatremia. However, in the current study we tried to adjust for a wide range of confounders. Still there was an increased risk in newly initiated tramadol and codeine usage. The supposed inhibition of the reuptake of noradrenaline and serotonin in tramadol usage, probably did not play a major role in inducing hyponatremia in our cohort since the adjusted risks were very similar between tramadol and codeine usage. The mechanism may still be mediated by the pharmacological effect of respective drug, such as an increased secreation of ADH.

However, there are other possible explanations to the present findings. Firstly, since pain by itself can induce SIADH [1,6], it cannot be ruled out that an incomplete blockade of nociceptive pathways causes SIADH in opioid treated individuals. Secondly, hypotension and nausea (secondary to opioid use) may also cause SIADH [28]. Thirdly, although adjusting for a broad range of concomitant drugs and diseases, the risk for residual confounding, in particular related to the pain condition, cannot be excluded.

In the current study, the risk of hospitalization due to hyponatremia was clearly higher in those newly initiated on tramadol or codeine. With few exceptions [20,27], most previous evidence on tramadol- and codeine-induced hyponatremia is based on case reports or case series [14–19], In a population-based cohort study by Fournier et al., following 332,880 patients initiating analgesic treatment over 14 years, tramadol was compared to codeine [20]. In this study, tramadol displayed a twofold increased risk of hospitalization for hyponatremia compared to codein [20]. On the contrary, we found similar risks for both tramadol and codeine. Besides differences in setting and study design, only 12 individuals on tramadol and 56 on codeine had been hospitalized with hyponatremia in the study by Fournier et al. compared to our 988 on tramadol and 944 on codeine in the current study. Consequently, the estimates of the former study were more uncertain with rather wide confidence intervals. Moreover, their definition of newly initiated therapy was 30 days compared to 90 days in our study.

This study has some further strengths and limitations not previously discussed. The major strength being the population-based approach which enabled us to include all patients admitted with the principal diagnosis of hyponatremia in the entire country during almost a decade. We did not have access plasma sodium levels, which is a limitation. However, by using the Swedish physicians' mandatory selection of principal diagnosis, we made sure only clinically relevant hyponatremia was taken into account. This is in contrast to studies including individuals with hyponatremia as a secondary diagnosis, diagnoses made in the secondary care [8], or patients with a mild to moderate hyponatremia regardless of symptoms [9]. Furthermore, we have previously validated the use of a principal diagnosis of hyponatremia and demonstrated that 89% had been hospitalized primarily due to symptoms of hyponatremia with mean plasma sodium level of 121 mmol/L [10]. Moreover, 77% of the population was exposed to levels below < 125 mmol/L [10], i.e., the level which defines profound hyponatremia [6], demonstrating further the clinical relevance of the outcome used.

There are several important clinical implications of the present study. In a patient requiring a weak opioid such as tramadol or codeine and with a history of hyponatremia or increased risk of hyponatremia, vigilance of hyponatremia symptoms is warranted and analysis of sodium levels should be performed for wide indications. Hospitalization due to hyponatremia usually occurs soon after initiation. Consequently, in a patient treated for more than three months, other causes are more likely to explain the onset of hyponatremia. The benefit/risk of withdrawing or switching the weak opioid should be considered carefully since this may result in worsening of the pain, which in turn may result in worse hyponatremia. Finally, the present study illustrates the importance of post marketing surveillance to reveal hitherto unrecognized properties that may be associated with a drug and to assess the real-world effectiveness and safety of the drug [30,31].

In conclusion, associations were found between tramadol or codeine usage and hospitalization due to hyponatremia which were markedly increased in those newly initiated. The risk was not increased during long-term use. The association may be causally related to the drugs, although an effect due to pain, nausea or the underlying disease cannot be excluded.

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Declaration of Competing Interest

Drs. Jakob Skov and Buster Mannheimer report consultancy fees from Otsuka Pharma Scandinavia AB, outside the submitted work. No other authors had any conflicts of interest.

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