Original Article

Non-thiazide diuretics and hospitalization due to hyponatraemia: A population-based case-control study

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Abstract

Objective: Diuretics are often implicated in hyponatraemia. While thiazides constitute one of the most common causes of hyponatraemia, data on loop diuretics and potassium-sparing agents are limited and partly conflicting. The objective of this investigation was to study the association between use of different types of non-thiazide diuretics and hospitalization due to hyponatraemia.

Design, Patients and Measurements: This was a register-based case-control study on the adult Swedish population. By linking national registers, patients hospitalized with a principal diagnosis of hyponatraemia (n = 11,213) from 1 October 2005 through 31 December 2014 were compared with matched controls (n = 44,801). Multivariable logistic regression, adjusted for multiple confounders, was used to analyse the association between use of diuretics and hyponatraemia. In addition, newly initiated use (≤90 days) and ongoing use were examined separately.

Results: Adjusted odds ratios (aORs) (95% CI) were 0.61 (0.57–0.66) for the use of furosemide, 1.69 (1.54–1.86) for the use of amiloride and 1.96 (1.78–2.18) for the use of spironolactone and hospitalization due to hyponatraemia. For newly initiated therapy, aORs ranged from 1.23 (1.04–1.47) for furosemide to 3.55 (2.75–4.61) for spironolactone. The aORs for ongoing use were 0.52 (0.47–0.57) for furosemide, 1.62 (1.47–1.79) for amiloride and 1.75 (1.56–1.98) for spironolactone.

Conclusions: Ongoing use of furosemide was inversely correlated with hospitalization due to hyponatraemia, suggesting a protective effect. Consequently, if treatment with furosemide precedes the development of hyponatraemia by some time, other causes of hyponatraemia should be sought. Spironolactone and amiloride may both contribute to hyponatraemia; this effect is most prominent early in treatment.

Keywords

adverse reaction, amiloride, furosemide, SIADH, sodium, spironolactone
Hyponatraemia, often defined as a serum sodium concentration below 135 nmol/L, results from an imbalance in water homeostasis, where the exchangeable sodium and potassium content in relation to total body water is decreased. Hyponatraemia is the most common electrolyte disorder, affecting up to one in three patients hospitalized. Acute symptomatic hyponatraemia is a rare and sometimes fatal disorder characterized by symptoms related to cerebral oedema, whereas the clinical panorama in chronic hyponatraemia ranges from fatigue and gait instability to mild cognitive deficits. Despite the paucity of severe symptoms, chronic hyponatraemia is a marker of poor outcome, with increased risk of death from underlying diseases.

Diuretics, which alter the excretion of both electrolytes and water, are often implicated in dysnatraemias. Despite considerable differences in molecular structures and sites of action in the nephron, ‘diuretics’ as a drug class are often implicated in hyponatraemia. Thiazide diuretics constitute the single most common cause of hyponatraemia, responsible for up to 25% of cases requiring inpatient care. In contrast, information on loop diuretics is partly conflicting. It is considered as a potential but rare cause of hyponatraemia but has also been used to treat hyponatraemia, with or without added supplementation of sodium chloride. Consequently, international guidelines consider loop diuretics as both potential cause of and remedy for hyponatraemia. For mineralocorticoid receptor antagonists and other potassium-sparing diuretics, data on hyponatraemia are limited.

Given the contradictory data on loop diuretics, and the limited information on potassium-sparing diuretics, the objective of this study was to explore how treatment with non-thiazide diuretics associates with the risk of hospitalization due to hyponatraemia.

This case-control study was conducted using data on the adult Swedish population from 1 October 2005 to 31 December 2014. Cases were defined as individuals, 18 years or older, hospitalized with a first-ever main diagnosis of hyponatraemia (E87.1) or SIADH (E22.2) according to the 10th revision of the International Classification of Diseases (ICD-10) in the National Inpatient Register (NPR). A first-ever diagnosis was defined as no previous main or secondary diagnosis of E87.1 or E22.2 dating back to 1 January 1997. For each case, four controls, individually matched for age, sex and municipality, without diagnostic records of hyponatraemia (since 1 January 1997), were identified in the Total Population Register (TPR), which contains data on birth, death, marital status and migration within Sweden and to and from other countries among other variables.

The index date of cases and their matched controls’ date were defined as the case’s date of hospitalization. A validation study of the principal diagnosis of hyponatraemia, with sodium levels corrected for plasma glucose, was performed in one of the larger hospitals. Variables of interest (diuretics) were identified by corresponding Anatomical Therapeutic Chemical (ATC) codes in the Prescribed Drug Register, which contains data on all prescription drugs dispensed in Sweden from 1 July 2005 onwards. Drug exposure was defined as a documented dispensing within 90 days prior to the index date, as most prescribed drugs in Sweden are filled in 3-month intervals. To explore time-dependent associations, drug exposure was further stratified into newly initiated versus ongoing treatment. Newly initiated use was defined as filled prescriptions within 90 days of the index day preceded by at least 12 months without filled prescriptions of the drug (91–454 days before the index date), whereas ongoing use required filled prescriptions in this time frame as well. Medications and medical conditions known or suspected to correlate with hyponatraemia and proxies for frailty were included in the statistical analysis as confounding factors. Adjustment for concurrent disorders was done from 1 January 1997 to the index date, with the exception of infectious diseases, which were adjusted for within 90 days before the index date. To adjust for socio-economic factors, parameters from the longitudinal integration database for health insurance and labour market studies were also taken into account. A complete list of variables is presented in Table 1.

The associations between individual drugs and hospitalization due to hyponatraemia were analysed by means of univariable and multivariable logistic regression. Associations for newly initiated and ongoing treatment were investigated in a multivariable model with exposure to each diuretic compound classified as ongoing, newly initiated or absent. Next, a sensitivity analysis excluding all cases and controls exposed to thiazides was performed. Associations were reported as unadjusted and adjusted odds ratios (ORs), with 95% confidence intervals (95% CI), p-values < .05 were considered statistically significant. For all analyses, R version 3.6.1 was used.

The study was approved by the Regional Ethical Review Board in Stockholm. Informed consent was waived.

During the study period, 11,213 adult individuals received a first-ever main diagnosis of hyponatraemia upon discharge from hospital. In addition, 44,801 matched controls were identified. The median age was 76 years (interquartile range: 65–84 years), with women accounting for 72%. Cases used more medications and were more likely to have a history of inpatient care compared with their matched controls. The most common comorbidities were hypertension, malignancies, ischaemic heart disease and diabetes (Table 1). Furosemide was used by 15.4% of cases and 12.1% of controls. For amiloride, the corresponding number was 13.3% of cases and 4.0% of controls. Spironolactone was used by 7.9% of cases and 2.9% of controls. In comparison, 38.9% of cases and 13.6% of controls were exposed to thiazides, whereas the use of other diuretics was negligible. Amiloride was typically...
used in combination with thiazide diuretics (97% of cases and 90% of controls on amiloride also used thiazides), whereas the use of thiazides was less common in combination with spironolactone or furosemide (<30% for cases and controls). The use of furosemide and spironolactone was associated with a greater burden of disease than the use of amiloride (Table 2).

Unadjusted ORs for exposure to diuretics and subsequent hospitalization due to hyponatraemia ranged from 1.31 (95% CI: 1.24–1.39) for furosemide, 2.84 (95% CI: 2.60–3.10) for spironolactone, to 3.83 (95% CI: 3.56–4.11) for amiloride. After adjustment for confounding factors, all ORs decreased, with furosemide demonstrating an inverse association with an OR of 0.61 (95% CI: 0.57–0.66), while the adjusted ORs for spironolactone and amiloride were 1.96 (95% CI: 1.78–2.18) and 1.69 (95% CI: 1.54–1.86), respectively (Figure 1).

In the time-dependent models, aORs for newly initiated use of drugs were higher compared with ongoing use for all diuretics. Of note, for furosemide, newly initiated use showed a weak but significant positive correlation with hyponatraemia (1.23; 95% CI: 1.04–1.47), whereas ongoing use was inversely associated with hospitalization due to hyponatraemia (0.52; 95% CI: 0.47–0.57) (Figure 2). In the sensitivity analysis, adjusted ORs differed slightly, with no increase in risk from newly initiated use of furosemide (aOR: 1.01; 95% CI: 0.89–1.15).

**TABLE 1  Medical characteristics and use of diuretics among cases and controls**

| Diuretics | Number (%) of total cases (n = 11,213) | Number (%) of total controls (n = 44,801) |
|-----------|---------------------------------------|-----------------------------------------|
| Furosemide | 1,722 (15.4) | 5,442 (12.1) |
| Amiloride  | 1,536 (13.7) | 1,783 (4.0) |
| Spironolactone | 886 (7.9) | 1,314 (2.9) |
| Thiazides  | 4,364 (38.9) | 6,103 (13.6) |

| Other medications | Number (%) of total cases (n = 11,213) | Number (%) of total controls (n = 44,801) |
|-------------------|---------------------------------------|-----------------------------------------|
| Antidepressants   | 2,817 (25.1) | 5,745 (12.8) |
| Antipsychotics    | 772 (6.9) | 1,096 (2.4) |
| Antiepileptic drugs | 1,061 (9.5) | 1,128 (2.5) |
| Antihypertensive drugs | 6,937 (61.8) | 19,173 (42.8) |
| Lipid-modifying agents | 2,314 (20.6) | 7,525 (16.8) |

| Diagnosis | Number (%) of total cases (n = 11,213) | Number (%) of total controls (n = 44,801) |
|-----------|---------------------------------------|-----------------------------------------|
| Malignancy | 3,096 (27.6) | 9,149 (20.4) |
| Ischaemic heart disease | 2,877 (25.7) | 8,787 (19.6) |
| Diabetes mellitus | 1,939 (17.3) | 5,277 (11.7) |
| Alcoholism | 1,764 (15.7) | 833 (1.9) |
| Cerebrovascular disease | 1,517 (13.5) | 3,574 (8.0) |
| Congestive heart failure | 1,453 (13.0) | 3,533 (7.9) |
| Hypothyroidism | 1,139 (10.2) | 1,994 (4.5) |
| Chronic obstructive pulmonary disease | 1,125 (10.0) | 1,576 (3.5) |
| Renal disease | 489 (4.4) | 888 (2.0) |
| Adrenal insufficiency | 460 (4.1) | 300 (0.7) |
| Liver disease | 421 (3.8) | 332 (0.7) |
| Pancreatic disease | 252 (2.2) | 395 (0.9) |
| Inflammatory bowel disease | 221 (2.0) | 444 (0.1) |

| Proxy for frailty | Number (%) of total cases (n = 11,213) | Number (%) of total controls (n = 44,801) |
|-------------------|---------------------------------------|-----------------------------------------|
| Number of dispensed drugs 90 days prior to index date | | |
| <4 drugs | 2,215 (19.8) | 22,892 (51.1) |
| 4–7 drugs | 3,421 (30.5) | 12,967 (28.9) |
| 8–12 drugs | 3,558 (31.7) | 7,010 (15.6) |
| >12 drugs | 2,019 (18.0) | 1,932 (4.3) |
| Number of hospitalizations ≥3 days duration | 4,852 (43.2) | 9,477 (21.2) |

*Data on bumetanide (n = 39), torasemide (n = 36) and eplerenone (n = 19) excluded due to low prevalence.

*Beta blockers, calcium channel blockers or agents acting on the renin-angiotensin system.
For amiloride, newly initiated therapy correlated with severe hyponatraemia, while ongoing therapy did not (Table 3).

4 | DISCUSSION

In this study on the adult Swedish population, we demonstrated considerable discrepancies in associations between different classes of non-thiazide diuretics and hospitalization due to hyponatraemia. Importantly, we found an inverse association between ongoing use of furosemide and hyponatraemia, suggesting a protective effect. This was not the case with newly initiated treatment. At the other end of the spectrum, the use of spironolactone and amiloride showed positive associations with hyponatraemia, most notably in the early course of treatment. However, for amiloride results should be interpreted with caution, as fixed-dose combinations with thiazides accounted for most prescriptions.

Pharmaceutical drugs are a common cause of hyponatraemia, and many drug classes have been implicated. For some drugs, such as thiazide diuretics, a true causal relationship is supported by numerous studies across different populations demonstrating a correlation, a profound effect on sodium levels in susceptible individuals and a clear temporal association. For other compounds, establishing causality is not as straightforward, when the underlying condition motivating treatment is also linked to hyponatraemia. This is often true for loop diuretics and spironolactone, which are used to...
treat diseases associated with hypervolaemic hyponatraemia (congestive heart failure, renal failure and liver failure). This may explain the persisting notion among clinicians of a correlation between furosemide and hyponatraemia, despite modest evidence in support of this perception. Loop diuretics exert their effect by blocking the Na-K-Cl cotransporter in the loop of Henle, thus reducing the reabsorption of these electrolytes. This leads to increased renal excretion of sodium, but also depletes the medullary osmotic gradient, reducing the capacity for water reabsorption in the collecting duct system. This in turn blunts the effect of antidiuretic hormone (ADH), reducing the risk of hyponatraemia through syndrome of inappropriate secretion of ADH (SIADH). Loop diuretics have in fact been identified as an independent risk factor for hypernatraemia in some studies.23,24 In the light of this, our findings of ongoing use of furosemide offering a moderate protection against severe hyponatraemia (aOR: 0.52) are perhaps not surprising. Similar effects have been observed for other drugs, most notably lithium, but antidiabetics and lipid-lowering agents have also been associated with a reduced risk of severe hyponatraemia, most likely through mechanisms promoting free water clearance, either through reduced sensitivity to ADH or by blunting the effect of ADH through other mechanisms.25–27 In the current study, odds ratios for exposure to amiloride dropped considerably after adjustment for confounders (OR: 3.83; aOR: 1.69). This was largely due to the fact that amiloride exerted its effects in the late distal tubule and collecting duct system in the nephron by inhibiting sodium reabsorption, leading to loss of both sodium and water. The diuretic effect is related to the levels of aldosterone, but typically modest. The drug has been associated with hyponatraemia in case reports,29 and in cohorts of patients with congestive heart failure30,31 and hypertension32 possibly due to hypovolaemic release of ADH in susceptible individuals. The reported frequencies are not directly comparable to our results (aOR: 1.96), but in the aforementioned studies, a modest drop in serum sodium appears to be more common than profound hyponatraemia. Plausible explanations to our findings include a partial effect of spironolactone as part of a multifactorial aetiology to profound hyponatraemia, or that previous studies have been underpowered to detect profound hyponatraemia resulting from spironolactone use. For reference, in a previous study on the present cohort the aOR for the use of thiazides in patients hospitalized due to hyponatraemia was 3.4 (95% CI: 3.2–3.7).9

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was mostly prescribed in fixed-dose combinations with thiazides during the study period. This is also the case in the literature, with reports on hyponatraemia and amiloride typically relating to the combined use of amiloride and thiazides\textsuperscript{22,33} or to potassium-sparing diuretics as a group.\textsuperscript{34} Nevertheless, adjusted odds ratios in our study suggested an association between severe hyponatraemia and amiloride.

Several limitations need to be addressed when interpreting our results. First, due to the inherent limitations of the case-control design, the associations described do not necessarily reflect causality. In addition, hyponatraemia is often multifactorial, with a combination of drugs and/or medical conditions contributing to low serum sodium concentrations. The use of diagnostic codes instead of serum sodium levels is a shortcoming. As mentioned in the methods section, we know from validation data that principal diagnoses of hyponatraemia are overwhelmingly correct, but they reflect severe hyponatraemia with a mean serum sodium 121 mmol/L\textsuperscript{15} and may not represent outcomes in terms of mild-to-moderate hyponatraemia. Still, defining cases by the use of diagnostic records ensured that the hyponatraemia encountered was considered clinically relevant, which in combination with the population-wide coverage was a major strength. Finally, despite adjusting for multiple confounding factors, residual confounding cannot be ruled out. For instance, the higher ORs observed for newly initiated versus ongoing treatment may in part relate to underlying disease (such as mild congestive heart failure) not yet diagnosed but still contributing to hyponatraemia.

To conclude, in this case-control study encompassing the adult Swedish population, we demonstrate an inverse association between hyponatraemia and amiloride.

CONFLICT OF INTEREST

J.S. and B.M. report previous consultancy fees from Otsuka Pharma Scandinavia AB, outside the submitted work. No other authors had any conflicts of interest.

AUTHOR CONTRIBUTIONS

B.M., H.F, J.L and J.S. conceived and designed the study, J.L. conducted statistical analyses. All authors interpreted the results. J.S wrote the manuscript, and all authors revised the manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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**SUPPORTING INFORMATION**

Additional supporting information may be found online in the Supporting Information section.

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