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Original Article

Associations of proton pump inhibitors and hospitalization due to hyponatremia: A population–based case–control study

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ABSTRACT

Background: Small observational studies and case reports have indicated that proton pump inhibitors (PPIs) may cause hyponatremia. Whether there is a difference between the individual PPIs is yet unknown. Since PPIs are one of the most commonly prescribed groups of drugs, even a rare adverse reaction may have large implications. The objective was to study the association between PPIs and hospitalization due to hyponatremia.

Methods: This register–based case–control study was based on the general Swedish population. Patients hospitalized with a principal diagnosis of hyponatremia ($n = 14{,}359$) were compared to matched controls ($n = 57{,}383$). The association between newly initiated (≤ 90 days) and ongoing PPI use was explored using multivariable logistic regression adjusting for concomitant drugs, medical conditions, previous hospitalizations and socioeconomic factors.

Results: Adjusted ORs (95%CI) for hospitalization due to hyponatremia, compared to controls, were for newly initiated: omeprazole 2.67 (2.37–3.01); pantoprazole 2.06 (1.32–3.19); lansoprazole 1.19 (0.72–1.94); esomeprazole 2.89 (2.21–3.79) and any PPI 2.78 (2.48–3.11). Only one individual had been newly initiated on rabeprazole and had been hospitalized due to hyponatremia. Adjusted ORs (95%CI) for individuals with ongoing treatment were for: omeprazole 1.04 (0.97–1.11); pantoprazole 0.81 (0.62–1.05); lansoprazole 0.90 (0.70–1.15); rabeprazole 3.34 (0.84–11.43); esomeprazole 1.12 (0.94–1.33) and any PPI 1.04 (0.98–1.11).

Conclusions: With the exception of lansoprazole, this study suggests an association between any newly initiated PPI-treatment and hospitalization due to hyponatremia. Ongoing PPI use was not associated with an increased risk.

1. Background

Hyponatremia is the most common electrolyte disturbance in hospitalized patients [1], giving rise to everything from mild, non-specific symptoms (fatigue, headache, and gait instability) to life-threatening symptoms (seizures, coma and death due to brain oedema) [2,3]. Drugs are frequently the culprit in mild hyponatremia but also in severe hyponatremia leading to hospitalization, with thiazide diuretics, antidepressants and antiepileptic drugs being the most common [4–6].

Proton pump inhibitors (PPIs) are among the most prescribed drugs worldwide [7,8], but have only rarely been claimed to cause hyponatremia [9]. However, drug companies marketing PPIs list hyponatremia as a rare adverse reaction (1/1000–1/10,000) in their product information for omeprazole and esomeprazole, an adverse reaction with unknown frequency for pantoprazole and rabeprazole, but not at all for lansoprozole (https://www.medicines.org.uk/emc). Yet, lansoprazole-induced hyponatremia has been reported [10]. Due to the considerable prescription of PPIs, even a rare adverse reaction may have large implications. The few published studies on PPIs and hyponatremia have mainly been case reports/series or smaller clinical observational studies [4,8,10–14]. This may cause issues for the treating physician. The aim of this study was to investigate the association between individual PPIs and the risk of hospitalization due to hyponatremia.

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2. Methods

This retrospective population–based case–control study was performed in Sweden. The principal diagnosis of an admitted patient is the best indicator of the condition that caused the hospitalization. In Sweden, each attending physician codes all admissions and specialist out-patient visits with *International Classification of Diseases* codes, 10th Revision (ICD10) [15]. Patients 18 years or older 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) between 1 October 2005 and 31 December 2014 were defined as cases. Four age-, sex- and municipality-matched controls (with no previous diagnosis of hyponatremia since 1 January 1997) per each case were randomly chosen from the Total Population Register. This study population has been reported on in detail in recent publications [5,6].

2.1. Variables

Variables, including their definition, incorporated in the multiple logistic regression analysis are presented in Table 1. To define potential confounders, 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. The definition of PPI exposure was a documented dispensation within 90 days prior to the index date, i.e., the date of hospitalization due to hyponatremia. Drug–dispensation is done every third month for long-standing therapy in almost all patients in Sweden. By using the ICD10 codes, chronic diseases were controlled for since 1 January 1997 to index date, except infectious diseases, which were controlled for within 90 days before the index date (Table 1). Newly initiated PPI therapy was defined as initiated within 90 days before the index date. In addition, the definition of ongoing PPI therapy required one or more dispensations in the period 91 to 454 days before the index date.

2.2. Data sources/measurement

By using the Swedish personal identification number, linkage between three population-based registers was performed: NPR, The Swedish Prescribed Drug Register (SPDR) and the LISA-register which encompasses socioeconomic data [15–17]. All hospitalizations in Sweden have been coded with ICD10 and stored in the NPR since 1997, while all prescriptions dispensed in Sweden have been stored in the SPDR since 1 July 2005. To adjust for socioeconomic factors the LISA register was used.

2.3. Statistical analysis

To analyse relationships between hospitalization due to hyponatremia and PPIs univariable and multivariable logistic regression was deployed. The reference group was persons not exposed to any of the drugs (last 90 days) or diagnosed with any of the diseases (since 1 January 1997) included in the model (see Table 1). The associations between severe hyponatremia and PPIs in cases and controls were presented as crude and adjusted (for potential confounders) odds ratios (OR), with 95% confidence intervals (95%CI). A P-value < 0.05 was defined significant. R version 3.3.2 was used for all calculations [18].

2.4. Ethical approval

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

Table 1
Included variables in the multiple logistic regression analysis and their definition.

Variables	Codes
	ATC codes beginning with
Proton pump inhibitors	A02BC, A02BD06
Omeprazol	A02BC01
Pantoprazol	A02BC02
Lansoprazol	A02BC03
Rabeprazol	A02BC04
Esomeprazol	A02BC05, A02BD06
Other drugs	
Carbamazepine	N03AF01
Oxcarbazepine	N03AF02
Phenytoin	N03AB02
Valproate	N03AG01
Lamotrigine	N03AX09
Levetiracetam	N03AX14
Gabapentin	N03AX12
Furosemide	C03C
Thiazides	C03A, C09BA, C09DA
Agents acting on the renin-angiotensin system	C09
Fluoroquinolones	J01MA
Macrolides	J01FA
Trimethoprim sulfamethoxazole	J01EE
SSRIs	N06AB
Other antidepressants	N06AX
Amiodarone	C01BD01
Tramadol	N02AX02
Desmopressin	H01BA02
Antipsychotic drugs	N05A
Diagnosis	**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	K50–51
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 mellitus	**ATC:** A10A, A10AB **ICD10:** E10-E14
Other factors	
Education	Increasing levels of education from 1 to 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
Duration of hospitalization	≥ 3 days

SSRIs, selective serotonin reuptake inhibitors.

Table 2
Medical characteristics (selection of items from Table 1) and different type of proton pump inhibitors among cases (hospitalized with a principal diagnosis of hyponatremia) and controls at index date.

	Number of total cases (n = 14,359)	Number of total controls (n = 57,382)
Diagnosis		
Hypertension	8818 (61.4%)	15,336 (26.7%)
Malignancy	3826 (26.6%)	11,231 (19.6%)
Ischemic heart disease	2808 (19.6%)	7880 (13.7%)
Diabetes mellitus	2423 (16.9%)	6581 (11.5%)
Alcoholism	2285 (15.9%)	1028 (1.8%)
Congestive heart failure	1900 (13.2%)	4493 (7.8%)
Cerebrovascular diseases	1884 (13.1%)	4540 (7.9%)
Chronic obstructive pulmonary disease	1477 (10.3%)	1958 (3.4%)
Adrenal insufficiency	821 (5.7%)	405 (0.7%)
Renal diseases	631 (4.4%)	1098 (1.9%)
Liver diseases	553 (3.9%)	417 (0.7%)
Pancreatic disease	327 (2.3%)	513 (0.9%)
Proton pump inhibitors, total		
Omeprazole	3354 (23.4%)	5729 (10.0%)
Pantoprazole	172 (1.2%)	314 (0.5%)
Lansoprazole	161 (1.1%)	365 (0.6%)
Rabeprazole	5 (0.03%)	8 (0.01%)
Esomeprazole	492 (3.4%)	663 (1.2%)
Any proton pump inhibitor	4015 (28.8%)	6977 (12.2%)
Proton pump inhibitors, newly initiated treatment		
Omeprazole	858 (6.0%)	808 (1.4%)
Pantoprazole	61 (0.4%)	53 (0.09%)
Lansoprazole	36 (0.3%)	66 (0.1%)
Rabeprazole	1 (0.007%)	0 (0%)
Esomeprazole	191 (1.3%)	133 (0.2%)
Any proton pump inhibitor	938 (6.5%)	891 (1.6%)

3. Results

During the study period of nine years, 14,359 individuals, 18 years or older, with a principal diagnosis of hyponatremia were identified together with 57,382 matched controls. Most were women (72%) and the median age was 76 years (range 18–103). A selection of medical conditions and the different PPIs in the study population at index date are presented in Table 2. Cases had more frequently been prescribed PPIs and were more likely to have chronic diseases. The most typical concomitant medical conditions were hypertension, malignancy, ischemic heart disease, diabetes and alcoholism, while the most commonly prescribed PPIs were omeprazole and esomeprazole, followed by lansoprazole, pantoprazole and rabeprazole.

The association between exposure to PPIs and hospitalization due to hyponatremia is depicted in Fig. 1. Adjusted ORs ranged from 1.01 for lansoprazole to 4.26 for rabeprazole, and for any PPI it was 1.25. Fig. 2 illustrates the associations (adjusted OR) after separating newly initiated PPI therapy from ongoing therapy. For newly initiated PPIs and newly developed hyponatremia requiring hospitalization, adjusted ORs ranged from 1.19 for lansoprazole to 2.89 for esomeprazole, and for any PPI it was 2.78. Only one individual had been newly initiated on rabeprazole and had developed hyponatremia resulting in hospitalization, thus calculation of OR was not meaningful. For ongoing treatment, the adjusted ORs were around one for all PPIs, except rabeprazole, and all were non-significant compared to controls. Thus, no association between PPIs and hospitalization for hyponatremia could be demonstrated when the PPIs had been used for more than three months.

4. Discussion

This is the first larger study reporting on the risk for hospitalization due to PPI-related hyponatremia. In addition, for the first time newly initiated vs. chronic use of different PPIs and severe hyponatremia has been explored. Overall, newly initiated PPI therapy increased the general risk for hospitalization due to hyponatremia with an adjusted OR of 2.78. However, the risk associated with lansoprazole was not significantly elevated compared to controls. Moreover, the risk increase associated with PPI use could no longer be discerned after three months of use.

Since previous studies on PPIs and hyponatremia have only been smaller observational studies or case reports, there have been no comparisons made between the different PPIs [4,8,10–13]. In the 63 elderly patients with severe hyponatremia (sodium $\leq$125 mmol/L) reported by Correia et al. the use of PPIs (not reported which PPIs) was more prevalent than in the 127 controls [12]. They did not adjust for confounders and the OR of 2.6 was very similar to our unadjusted OR of 2.8 for all PPIs. Also, the study by Buon et al. of 145 hospitalized elderly patients of whom 24 had moderate hyponatremia demonstrated increased risk for hyponatremia by PPI use (OR 4.4) [11].

Our main finding was the increased risk of hospitalization due to hyponatremia after newly initiated PPI therapy. In contrast, lansoprazole did not demonstrate an elevated risk. Yet, a case report of lansoprazole-induced hyponatremia has been published [10], but this drug seemed safe overall from hyponatremia. Newly commenced pantoprazole had an increased risk in our study but there have only been two previous case reports of pantoprazole-induced hyponatremia.[13,14] Only one individual had been newly started on rabeprazole and this person had developed hyponatremia requiring hospitalization. In the published literature we could not find any previous report on rabeprazole-induced hyponatremia. However, hyponatremia is listed as an adverse reaction with unknown frequency in the product information of rabeprazole (https://www.medicines.org.uk/emc/product/3804/smpc). Since only 12 out of 71,741 individuals included in our study had used rabeprazole, all findings with this drug should be interpreted with caution. Newly initiated omeprazole and its enantiomer esomeprazole were found to be associated with hospitalization due to hyponatremia with ORs just below 3. Since these two drugs by far were the most prescribed PPIs in the current study, these findings were probably the most robust. Most previous literature on PPI-induced hyponatremia has been on either omeprazole or esomeprazole [8]. Interestingly, the increased risk of hospitalization due to PPI-induced hyponatremia was no longer evident during long-term use. Similar patterns have recently been found by us in antidepressant–related [5] and anti-epileptic drug-related severe hyponatremia [6]. It could be speculated that individuals predisposed for drug-related severe hyponatremia had to cease the treatment shortly after PPI initiation, leaving patients on PPIs that are less susceptible. However, this is an unlikely explanation, since PPI-induced hyponatremia is not well-known among physicians. This temporal association between initiation of PPI and hyponatremia admission increases the likelihood of a genuine underlying relationship, which is seldom established in hyponatremia. There are several clinical implications by this study. In patients with a history of hyponatremia or susceptible with a concomitant treatment known to be associated with a risk of hyponatremia, lansoprazole may be considered. If a symptomatic hyponatremia resulting in hospitalization develops after recent initiation of rabeprazole, esomeprazole, omeprazole or pantoprazole, lansoprazole could be an alternative management. However, once PPIs have been prescribed for more than three months they seemed to be relatively safe from a severe hyponatremia point of view. This is in contrast to the above mentioned study by Buon et al. which only examining long-term PPI use (> 1 year) and hyponatremia [11], but this study had only 24 individuals with hyponatremia, many of them without PPI use, making the interpretations very uncertain. The benefit/risk of stopping PPI should be considered with knowing risk that stopping PPI is associated to a risk of major bleeding [19].

SIADH is believed to be the major cause of PPI-induced hyponatremia [4]. However, renal salt-wasting has also been suggested, since PPIs are the most frequent cause of drug-induced acute interstitial nephritis [4,8], but this is probably more unlikely. Whether a peripheral

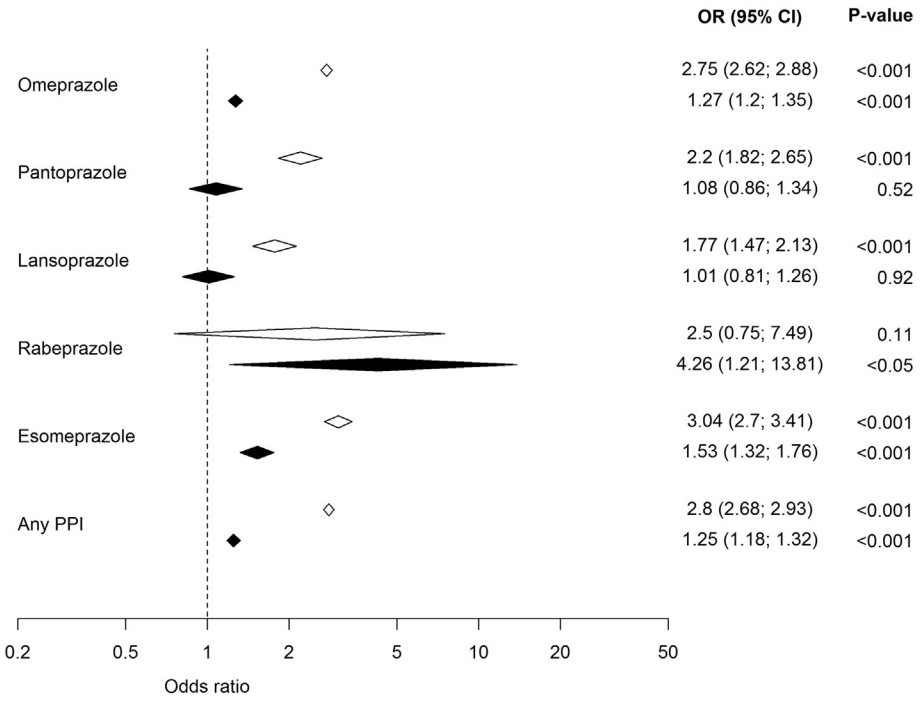

Fig. 1. The crude (white) and adjusted (black, all variables in Table 1) odds ratio (OR), including 95% confidence intervals (95% CI) for hospitalization due to hyponatremia in patients on different proton pumps inhibitors (newly/ongoing).

process (such as a direct effect renal tubular ion exchange) could be a contributing factor to the difference in PPI-induced severe hyponatremia between the individual PPIs remains speculative.

Our study has several limitations, but also strengths. We did capture all cases admitted in Sweden with a principal diagnosis of hyponatremia during a period of nine years, but the number of cases for some individual PPIs, especially rabeprazole, was nevertheless relatively small. Although we did examine the relative risks of newly initiated PPIs, the case–control design restricts the prospect of exploring the importance of the treatment duration. A longitudinal cohort study could investigate this more thoroughly and would also allow analysis of absolute risks (incidences) associated with PPIs. Adjustment for a wide

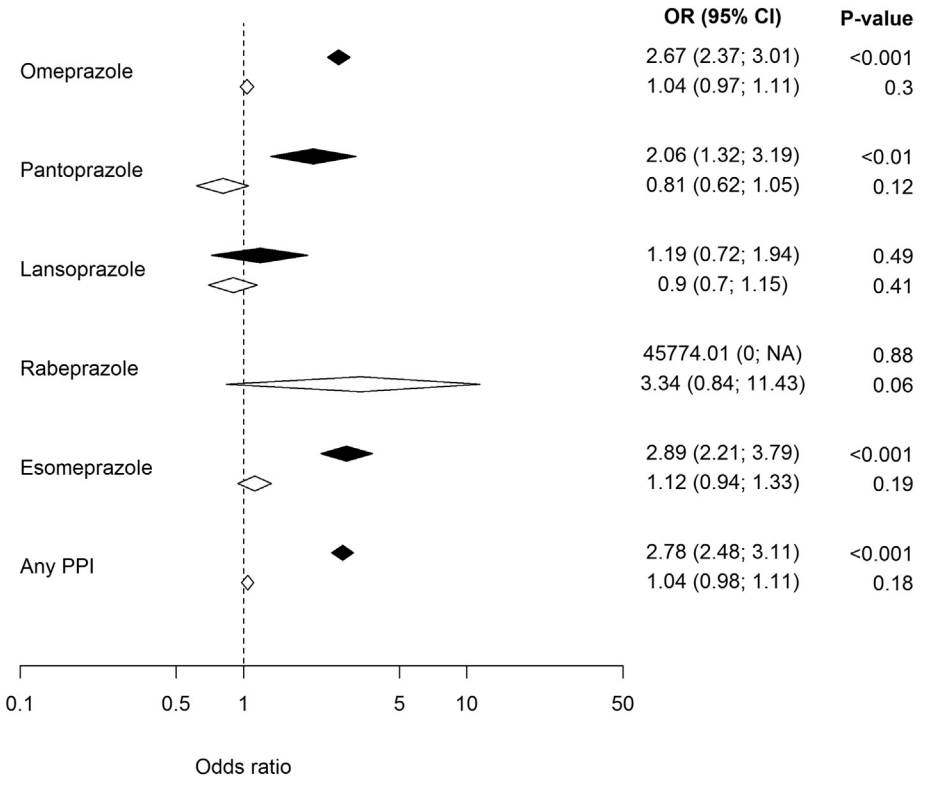

Fig. 2. The odds ratio (OR), including 95% confidence intervals (95% CI) for hospitalization due to hyponatremia in patients with ongoing (white) and newly initiated proton pump inhibitor therapy (black). All ORs have been adjusted for the confounding factors in Table 1. Newly initiated rabeprazole could not be shown since only one individual had been newly initiated on this therapy and this patient had been hospitalized due to hyponatremia.

range of drugs, diagnoses and socioeconomic factors was performed. However, there may still be other residual confounding factors not taken into account of. Lastly, we did not have access to the exact plasma sodium levels. Nevertheless, since we only included patients admitted with a principal diagnosis of hyponatremia we know that the hyponatremia was severe and the specificity of a principal diagnosis is by far superior to an outcome that also includes secondary diagnoses (www.socialstyrelsen.se/Lists/Artikelkatalog/Attachments/18692/2012-4-18.pdf). This is in accordance with our previously validation study demonstrating that 100% of patients having a principal diagnosis of hyponatremia had severe hyponatremia with a mean plasma sodium level of 121 mmol/L [5]. Thus, the specificity of ICD-codes to detect hyponatremia is excellent since all have low plasma sodium levels, but the sensitivity is low. Due to the study design using data from different registers, specific symptoms and signs associated with hyponatremia (e.g. confusion, altered mental state, changes in seizures frequency) at admission could not be explored. Nevertheless, our validation study demonstrated that 89% had been admitted primarily due to symptoms of hyponatremia [5]. An additional strength of the current study, besides including only clinically relevant hyponatremia, is the unique Swedish personal identification number, which permitted unambiguous linkage between population-based registers with virtually complete coverage. Furthermore, adjustments for a large number of factors that could contribute to hyponatremia were performed to better estimate the contribution of the PPIs. Finally, thanks to the large size of this study, comparisons between a wide range of individual PPIs could be made.

In conclusion, with the exception of lansoprazole, this study suggests an association between any newly initiated PPI-treatment and hospitalization due to hyponatremia. Ongoing PPI use was not associated with an increased risk.

Conflicts of interest

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

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