

Association between antidepressant drug use and hyponatraemia: a case-control study

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Aims To estimate the risk of, and risk factors for, hyponatraemia associated with the use of selective serotonin reuptake inhibitors (SSRIs) compared with the use of other antidepressant drugs.

Methods A case-control study of psychiatric in- and out-patients on antidepressant drugs performed in the mid-southern part of The Netherlands over a 2 year period. Cases ($n=29$) were all using antidepressant drugs with a serum sodium concentration of ≤ 130 mmol l⁻¹ while controls ($n=78$) were patients on antidepressants with a normal sodium concentration (136–144 mmol l⁻¹). Information on blood sodium concentrations was obtained from clinical chemistry data while information on drug use was obtained from community and hospital pharmacy databases. Medical records were used to ascertain possible risk and confounding factors. Unconditional multivariate logistic regression was used to estimate odds ratios for hyponatraemia in patients on SSRIs compared with patients on other antidepressant drugs.

Results SSRIs were associated with an increased risk of hyponatraemia (OR 3.3; 95% CI 1.3, 8.6) compared with other classes of antidepressant drugs. Stratified and interaction analyses revealed that elderly patients using diuretics concomitantly with SSRIs were at the highest risk of experiencing hyponatraemia (OR 13.5; 95% CI 1.8, 101).

Conclusions SSRIs are more frequently associated with hyponatraemia than other classes of antidepressant drugs. This adverse drug reaction was more common in older patients (≥ 65 years) and in those using diuretics.

Keywords: antidepressants, hyponatraemia, pharmacoepidemiology, SSRI

Introduction

Hyponatraemia can cause significant morbidity, such as lethargy, headache, confusion, convulsions, coma, and can occasionally cause death [1, 2]. The clinical symptoms of hyponatraemia are, however, variable and depend mainly on its severity and abruptness of onset. Signs and symptoms of hyponatraemia generally do not appear until the serum sodium concentration falls below 130 mmol l⁻¹

and, in chronic hyponatraemia, approximately 50% of the patients are asymptomatic even with serum sodium concentrations lower than 125 mmol l⁻¹ [3]. In the range of 125–130 mmol l⁻¹, the predominant symptoms are gastrointestinal; once the serum sodium falls below 125 mmol l⁻¹, neuropsychiatric symptoms predominate [2]. The mortality rate is high when serum sodium levels drop acutely below 120 mmol l⁻¹, but not when the progression is slow.

Hyponatraemia is known to be associated with many different drugs including diuretics, antiepileptics and psychotropic drugs [4–7]. Hyponatraemia associated with use of antidepressant drugs has been described in several case reports and case series [8–10]. There have also been numerous recent case reports of an association between the use of selective serotonin reuptake inhibitors

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(SSRIs) and hyponatraemia [11–13]. In the WHO-database of adverse drug reactions, most reports of SSRI-related hyponatraemia were due to fluoxetine, paroxetine and sertraline (821, 400 and 219 reports until July 1998, respectively) [14].

Hyponatraemia is known to be a relatively frequent form of electrolyte disturbance amongst psychiatric patients [5, 15–17]. In a case-control study, Siegler and colleagues [18] investigated risk factors for the development of hyponatraemia in psychiatric inpatients. After adjustment for potential confounders, they found that use of fluoxetine and tricyclic antidepressants (TCAs) was significantly associated with hyponatraemia, with fluoxetine showing a higher risk than TCAs. Therefore, it is not clear from this study whether fluoxetine is uniquely associated with hyponatraemia or whether other serotonin reuptake inhibitors also increase risk.

The objectives of the present study were to estimate in psychiatric in- and out-patients, the risk of hyponatraemia associated with the use of SSRIs in comparison with other antidepressant drugs, and to identify additional risk factors that predispose patients to developing hyponatraemia.

Methods

Setting

The study was conducted in co-operation with two general teaching hospitals offering out- and in-patient psychiatric services, and a large mental health centre located in the city of Tilburg, The Netherlands, covering a population of approximately 350 000 persons. The source populations of our study were all psychiatric in- and out-patients on antidepressants throughout the period from June 1997 until June 1999. Subjects were identified from a database containing laboratory data on sodium blood concentrations. In the Tilburg region, all biochemical laboratory data from in- and out-patients are recorded in a database available from one single clinical chemistry and haematology laboratory. Drug prescription data for all patients were obtained from community and hospital pharmacies. Data on (co)morbidity were obtained from medical records. All data relating to the patients were anonymously provided and the Medical Ethics Committees of all participating institutions approved the study protocol.

Study design

A case-control design was used to assess the relationship between the use of SSRIs in comparison with the use of other antidepressant drugs and the occurrence of hyponatraemia. Case and control patients (study population) were selected from the laboratory database over

a 2 year period from June 1997 until June 1999. Subjects were excluded if they were younger than 18 years of age.

Cases

Cases included all individuals in the source population who experienced at least one period of hyponatraemia within the study period. Hyponatraemia was defined as a serum sodium concentration of ≤ 130 mmol l⁻¹. The index date was defined for each case as the calendar date on which the serum sodium concentration was ≤ 130 mmol l⁻¹ for the first time. Patients were defined as antidepressant drug 'users' if the prescription for one or more antidepressants lasted until the index date. Case patients were counted only once even if they had two or more periods of hyponatraemia during the study period.

Controls

For each case, if possible, three matched control patients were randomly selected from the source population matched for serum sampling date (within a maximum of 5 days from the case index date) and (admission) ward as marked in the computerized profile of the patients. Control patients were defined as those patients with a sodium serum concentration between 136 and 144 mmol l⁻¹. Subjects with sodium concentrations between 131 and 135 mmol l⁻¹ were excluded to ensure a clear contrast between cases and controls.

Potential confounders

In order to adjust for factors that may confound the association between the use of SSRIs and the occurrence of hyponatraemia, additional data on concomitant medication (diuretics, ACE inhibitors, calcium channel blockers, nitrates, β -adrenoceptor blockers, antipsychotics, benzodiazepines and anti-epileptics) and (co)morbidity (diabetes mellitus, hypertension, heart failure, coronary artery disease, history of myocardial infarct, renal function parameters, COPD, lung carcinoma and smoking) were collected. From the prescription drug histories of each patient, the concomitant medication used on the index date was determined. To define the use of concomitant drugs, the same time window was used as for the antidepressants. Data on (co)morbidity were obtained from the medical records as well as from a complete computerized hospital discharge database. Diagnoses of (co)-morbidity were defined by the International Classification of Diseases (9th edition).

Data analysis

For both cases and controls the prevalence of each characteristic on the index date was determined. An ANOVA/Student's *t*-test was performed to assess the significance of differences in the mean of continuous variables

between cases and controls. Differences in proportions of categorical variables between cases and controls were tested for significance by a Chi-square test. To estimate the association between antidepressant drug use or any other potential risk factor and hyponatraemia, crude and adjusted odds ratios (OR) with 95% confidence intervals (95% CI) were calculated using logistic regression. Data on (co)morbidities were not available for all subjects. For those missing values, dummy variables for presence of data were created and entered into the multivariate logistic model. Stratified analysis was used to identify high-risk patients. In addition, stratified and interaction analysis was used to estimate and test for synergistic effects between the risk factors. All statistical calculations were carried out with the SPSS statistical package (version 9.0).

Results

The total number of patients registered during the study period who had had a sodium serum concentration measured was 39 071. A total of 1391 patients had a serum sodium ≤ 130 mmol l⁻¹ and were considered as potential cases (3.6%). Overall, from this source population, 29 subjects (2.1%) were identified as having developed hyponatraemia (serum sodium ranged from 104 to 130 mmol l⁻¹) while on antidepressant drug therapy, and 78 subjects with normonatraemia (i.e. controls) were sampled. Twenty-two patients (76%) with hyponatraemia were current users of selective serotonin reuptake inhibitors (SSRIs) whereas among the control patients, the percentage of current SSRI users on the index date was 49% (38 out of 78). SSRI users had a three times higher risk (unadjusted odds ratio 3.3 [95% CI 1.3, 8.6]), for developing hyponatraemia in comparison with users of other antidepressant drugs.

Baseline characteristics of, and differences between, cases and controls are summarized in Table 1. The gender distribution of the cases did not differ from those of controls; however, case patients were older than control subjects (68 and 57 years, respectively). There was no clinically important difference between cases and controls in renal function, with respect to serum creatinine and blood urea nitrogen.

The medications and diseases known to be associated with hyponatraemia were recorded for both case and control patients. The results of the logistic regression analyses controlled for potential confounding variables are presented in Table 2. After adjustment for potential confounding, there was a clear association between hyponatraemia and the use of SSRIs compared with other antidepressants (OR_{adjusted} 3.9; 95% CI 1.2, 13.1). More than half (55%) of all prescriptions of antidepressant drugs at the index date were attributed to paroxetine (OR_{adjusted} 5.1; 95% CI 1.5, 17.2).

Other strong risk factors for hyponatraemia were an abnormal potassium level (>5.0 mmol l⁻¹) (OR_{adjusted} 24; 95% CI 2.0, 283) and older age. Older patients (≥ 65 years) had more than six fold increased risk for hyponatraemia than younger patients (OR_{adjusted} 6.3; 95% CI 1.0, 41). Although the crude odds ratio for lung carcinoma was high (OR 4.7; 95% CI 0.7, 30), the difference was not statistically significant. Patients using β -adrenoceptor blockers or those suffering from diabetes mellitus had an unadjusted, 2.6 (95% CI 1.0, 6.9) and 3.0 (95% CI 1.0, 9.3) fold higher risk for developing hyponatraemia, respectively. However, after adjustment, none of these odds ratios remained statistically significant. Smoking was (OR 0.7; 95% CI 0.3, 1.8) not significantly associated with hyponatraemia.

Stratified analysis and statistical tests for interaction were performed for those characteristics that were most likely to demonstrate an additive risk for hyponatraemia (Table 3). The analysis showed a synergistic effect for the concurrent use of SSRIs and diuretics compared with nonuse (OR 8.4; 95% CI 2.1, 34). This effect was even more pronounced in the elderly patients (age ≥ 65 year), who showed the highest risk (OR 13.5; 95% CI 1.8, 101) for developing hyponatraemia.

Discussion

Our results show that users of SSRIs in daily clinical practice have an approximately four times higher risk for developing hyponatraemia compared with users of other antidepressant drugs. Elderly patients concomitantly using diuretics fall into the highest risk category.

Prior evidence for the association between antidepressants and hyponatraemia mainly stems from case reports. Another pharmacoepidemiological study including a control group has been conducted and showed that patients using fluoxetine had a higher risk for developing hyponatraemia compared with patients using no antidepressant drugs [18]. However, this study did not clarify whether the high risk for developing hyponatraemia was specific to fluoxetine, or whether the effect was common to all SSRIs. Our results do show that paroxetine is strongly associated with hyponatraemia. Taken together with other studies and case reports, the data strongly suggest that SSRIs as a class cause hyponatraemia more frequently than other antidepressant drugs.

From the literature, it is known that hyponatraemia is strongly associated with elderly patients. In an ambulatory geriatric population, Miller and coworkers [19] found that 11% of the patients were hyponatraemic (serum sodium less than 135 mmol l⁻¹). Bouman and colleagues [20] studied hyponatraemia in a group of older patients (mean age 77 year) admitted to a psychiatry ward. They found the incidence of hyponatraemia (serum sodium less than

Table 1 Characteristics of case and control patients.

	Cases (n = 29)	Controls (n = 78)	OR (95% CI) or P value
<i>Demographics</i>			
Age (years), mean \pm s.d.	68 \pm 14	57 \pm 18	
Age-category n (%):			
\leq 45 years	2 (7)	21 (27)	1.0 (reference)
45–64 years	8 (28)	27 (35)	3.1 (0.60, 16.2)
\geq 65 years	19 (65)	30 (38)	6.6 (1.4, 32)
Sex n (%)			
Male	10 (35)	32 (41)	1.0 (reference)
Female	19 (65)	46 (59)	1.3 (0.5, 3.2)
Sodium (mmol l ⁻¹)			
\leq 120	6 (21)
121–125	4 (14)
126–130	19 (65)
Creatinine (μ mol l ⁻¹), mean \pm s.d.	88 \pm 44	85 \pm 36	0.732
Blood urea nitrogen (mmol l ⁻¹), mean \pm s.d.	6.4 \pm 3.6	6.0 \pm 2.9	0.623
Potassium (mmol l ⁻¹), mean \pm s.d.	4.46 \pm 0.63	4.20 \pm 0.43	0.017
<i>Exposure n (%)</i>			
Serotonin reuptake inhibitors	22 (76)	38 (49)	3.3 (1.3, 8.6)
Paroxetine	21 (69)	31 (40)	4.0 (1.6, 10.1)
Diuretics	11 (38)	18 (23)	2.0 (0.8, 5.1)
Angiotensin converting enzyme inhibitors	7 (24)	9 (12)	2.4 (0.8, 7.3)
Calcium channel blockers	5 (17)	9 (12)	1.6 (0.5, 5.2)
Nitrates	1 (3)	5 (6)	0.5 (0.1, 4.7)
β -adrenoceptor blockers	10 (35)	13 (17)	2.6 (1.0, 6.9)
Antipsychotics	6 (21)	23 (30)	0.6 (0.2, 1.7)
Benzodiazepines	16 (55)	37 (47)	1.4 (0.6, 3.2)
Anti-epileptics	3 (10)	4 (5)	2.1 (0.4, 10.2)
<i>Co-morbidity n (%)</i>			
Diabetes mellitus	7 (26)	8 (10)	3.0 (1.0, 9.3)
Hypertension	5 (19)	18 (23)	0.7 (0.2, 2.2)
Heart failure	4 (15)	7 (9)	1.7 (0.5, 6.5)
Coronary artery disease	12 (43)	21 (27)	2.0 (0.8, 4.9)
Myocardial infarct	4 (15)	11 (14)	1.0 (0.3, 3.6)
Chronic obstructive pulmonary disease	4 (15)	13 (17)	0.9 (0.3, 2.9)
Lung carcinoma	3 (11)	2 (3)	4.7 (0.7, 29.7)
Current smoking	8 (30)	29 (38)	0.7 (0.3, 1.8)
Abnormal potassium (>5.0 mmol l ⁻¹)	5 (17)	1 (1)	16 (1.8, 143)

135 mmol l⁻¹) to be 25% following the prescription of an SSRI. Our results support Bouman's report [20] that people older than 65 years of age are at particularly high risk of developing hyponatraemia when using SSRIs.

Our results that gender was not statistically significantly associated with hyponatraemia contradict the results reported in the literature. It has been postulated that women are at greater risk of hyponatraemia, for which there may be several contributory factors [10]. Female patients may have increased exposure to SSRIs because the incidence of appropriate indications is increased in the female population, and as described by Egberts and others [21], women are more likely to receive SSRIs than men in a community-based population, which may confound the association.

Surprisingly, we did not find a strong significant correlation between the use of diuretics and the occurrence of hyponatraemia, an association that has been described in various reports [6, 18]. However, data from large clinical trials, e.g. stroke prevention due to antihypertensive drugs, did not explicitly show thiazide-induced hyponatraemia [22]. Angiotensin converting enzyme inhibitors, calcium channel blockers, and β -adrenoceptor blockers are also risk factors for the development of hyponatraemia [18]. In our study, angiotensin converting enzyme inhibitors, calcium antagonists and β -adrenoceptor blockers showed an increased risk for hyponatraemia; however, these results were not statistically significant.

From the literature, it has been hypothesized that smoking is negatively associated with hyponatraemia [23].

Table 2 Crude and adjusted odds ratios of the risk factors for hyponatraemia.

Risk factors	Crude OR (95% CI)	Adjusted* OR (95% CI)
Selective serotonin reuptake inhibitors	3.3 (1.3, 8.6)	3.9 (1.2, 13.1)
Paroxetine	4.0 (1.6, 10.1)	5.1 (1.5, 17.2)
Age (≥ 65 years)	6.6 (1.4, 32)	6.3 (1.0, 41)
β -adrenoceptor blockers	2.6 (1.0, 6.9)	2.6 (0.7, 10.0)
Diabetes mellitus	3.0 (1.0, 9.3)	1.6 (0.4, 6.7)
Lung carcinoma	4.7 (0.7, 30)	6.5 (0.6, 71)
Potassium (>5.0 mmol l ⁻¹)	16 (1.8, 143)	24 (2.0, 283)

OR = odds ratio.

*Adjusted for age, gender, diabetes mellitus, lung carcinoma, use of β -adrenoceptor blockers and serum creatinine and potassium (>5 mmol l⁻¹).

Table 3 Interaction between current use of selective serotonin reuptake inhibitors and current use of diuretics compared with nonuse of either drug.

Age ≥ 65 years	Crude OR	Adjusted* OR
Nonuse	1.0 (reference)	1.0 (reference)
Only SSRIs	3.2 (0.51–19.3)	6.2 (0.4–97)
Only diuretic	0.56 (0.1–7.4)	0.98 (0.01–61)
Both SSRI and diuretic	13.5 (1.8–101)	148 (5.4–4145)

SSRI = selective serotonin reuptake inhibitor.

OR = odds ratio.

*Adjusted for age, gender, diabetes mellitus, lung carcinoma, use of β -adrenoceptor blockers and serum creatinine and potassium (>5 mmol l⁻¹).

Our data support this suggestion, although the result failed to achieve statistical significance. Nicotine is known to be a potent stimulator of vasopressin and is thus a potential cause of hyponatraemia due to the physiological effect of enhancing water reabsorption in the collecting ducts of the kidneys [24]. Disorders of water homeostasis due to either compulsive water drinking or the syndrome of the inappropriate antidiuretic hormone secretion (SIADH) are common in psychiatric patients, and are characterized by hyponatraemia [24].

Patients with small cell lung cancer due to ectopic production of antidiuretic hormone are known to develop SIADH and severe hyponatraemia [25–27]. Our study confirms this finding (Table 2); however, probably due to the small size of the population no statistical significance was reached. None of the patients with lung cancer was treated with antineoplastic therapy, which can also cause hyponatraemia.

An important finding of our study was the synergistic effect of diuretics and SSRIs, as previously suggested in case reports. From the results, it is clear that older

patients concomitantly using SSRIs and diuretics have a strongly increased risk for hyponatraemia compared with patients using both agents separately. This suggests that clinicians should be aware that elderly patients who are on both SSRIs and diuretics, and present with non-specific (neuropsychiatric) symptoms like confusion, lethargy, or vomiting may indeed have hyponatraemia.

There are several limitations to our study. In general, a major concern in case-control studies is the possibility of information bias. However, recall bias was unlikely to occur because we used data that had already been gathered before the onset of hyponatraemia. To minimize observer bias at the time of data collection, comorbidity data were gathered in two different ways: by using the paper patient records as well as the automated hospital database containing all patients' diagnoses (coded by ICD-9). A second concern is the possibility of selection bias. In our study, all patients with a sodium serum level ≤ 130 mmol l⁻¹ were checked for antidepressant drug use. Control patients were chosen from a patient population admitted to the same ward in order to minimize the risk for bias by indication. All patients were selected from the automated laboratory database. Clearly, the symptoms of hyponatraemia are often nonspecific and therefore not always looked for; often it is only detected accidentally by routine laboratory testing. From this point of view, it is not likely that patients using SSRIs are more frequently tested for blood sodium levels than users of other antidepressant drugs. In addition, blood sodium was measured by the same laboratory for both out- and in-patients.

Another limitation of this study is the sample size. The number of cases in this study was small, and therefore, we could not show a statistically significant difference between case and control patients for use of single antidepressants as well as several potential confounders. However, all confounding variables known to be associated with hyponatraemia were quantified. We were unable to control for confounding variables, which were not measured in this nonexperimental study.

Unfortunately we were not able to determine the average time to onset of hyponatraemia because it was not possible to delineate the initial dates of therapy for all patients. However, according to the literature, hyponatraemia induced by antidepressants can occur from within 1 day to several months after the initiation of drug therapy. Liu and others described a median onset of 13 days [12]. However, there was a wide range in the time frame; in 29% of the patients hyponatraemia was diagnosed >3 months after starting SSRI therapy. Kirchner and coworkers also noted a wide range of time to detection from 1 to 253 days with a mean time to detect hyponatraemia following SSRI initiation of approximately 3 weeks [28]. Most data used in these reviews

describing this time relation were from unpublished reports. In a prospective study of 14 cases of SSRI-induced hyponatraemia, the median time to onset was almost 14 days [14].

Our study overcomes some of the methodological difficulties of previous work. We assessed the risk of hyponatraemia in relation to the use of antidepressant drugs in a large representative psychiatric population under everyday circumstances. This is in contrast to the study of Siegler and others who investigated a tertiary inpatient psychiatric population [18]. Wilkinson and others studied a relatively old population in which they determined an incidence for SSRI-induced hyponatraemia of about 3–5 new cases per 1000 patients treated per year [14]. However, in their study it was not possible to calculate a relative risk for hyponatraemia because all cases as well as all control patients had been using SSRIs. Furthermore, prior evidence was mainly obtained from uncontrolled case reports and case series.

The pathogenesis of hyponatraemia in patients treated with antidepressants in general and with SSRIs specifically is unknown. Some animal studies have shown that serotonergic mechanisms are involved in the regulation of antidiuretic hormone secretion [29, 30]; however, this finding was not confirmed in another study [31]. The syndrome of inappropriate antidiuretic hormone secretion has often been mentioned in case reports as the cause of antidepressant-associated hyponatraemia. Further research is needed to delineate the mechanism through which antidepressants cause hyponatraemia.

In conclusion, our study indicates that users of SSRIs in comparison with other antidepressants have a higher risk for developing hyponatraemia. The elderly and those simultaneously using diuretics have the highest risk for this serious and potentially deadly adverse drug reaction. Physicians should be aware of SSRI-induced hyponatraemia in daily clinical practice, and we would advise that serum sodium concentrations are measured on a regular basis.

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