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PHARMACOEPIDEMIOLOGY AND PRESCRIPTION

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Serotonergic antidepressants associated with an increased risk for hyponatraemia in the elderly

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Abstract *Background*: Hyponatraemia may have serious clinical consequences. Several reports of hyponatraemia associated with the use of antidepressants have been published. However, it remains unclear whether a specific class or individual antidepressants are associated with an increased risk for hyponatraemia.
Objectives: To investigate the association between the use of serotonergic antidepressant drugs and the occurrence of hyponatraemia compared with non-users of these agents and to determine the time-to-admission rate after initiation of these drugs.
Method: A matched case-control study was conducted. Data were obtained from the PHARMO database including information on drug dispensing and hospital admission indications for 320,000 inhabitants of eight Dutch cities. Data from 1990 to 1998 were used. Case patients ($n = 203$) were all patients who were admitted to a hospital for hyponatraemia. Community controls ($n = 608$), matched by age and gender, were sampled within the same living area and calendar (index) date as the case patients. All patients were 18 years of age or older. Exposure to antidepressant drugs, classified as serotonergic versus non-serotonergic agents, and potential confounding factors were determined on the index date. Time-to-admission was defined as the period between start of the antidepressant drug and hospital admission. Conditional logistic regression model was used to estimate odds ratios (ORs) and to adjust for potential confounding factors.
Results: Ten (5%) case patients used serotonergic antidepressants compared with eight (1%) in the control group; compared with non-use, the risk for hyponatraemia was fourfold higher [OR 3.96; 95% confidence interval (CI) 1.33, 11.83] due to serotonergic antidepressant drug use. Risk for developing hyponatraemia was greatest in the first 2 weeks of serotonergic drug therapy.
Conclusion: Use of serotonergic antidepressants is associated with the development of hyponatraemia. Hyponatraemia occurred during the first 2 weeks of treatment, which justifies blood-sodium monitoring during the first weeks after initial treatment with a serotonergic antidepressant.

Keywords Serotonergic antidepressants · Hyponatraemia · Elderly

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Introduction

Selective serotonin-reuptake inhibitors (SSRIs) are among the most widely prescribed central nervous system drugs in the world and have been available in The Netherlands since the 1990s. These drugs are often considered as safe first-line therapy in the treatment of several psychiatric illnesses. In a review article, Kirby and Ames [1] recently examined SSRI-induced hyponatraemia as an increasingly recognised possible side effect in clinical practise.

The clinical relevance of hyponatraemia is, however, variable and depends mainly on its degree and abruptness of onset [2]. It often is asymptomatic, but may also result in serious neurological problems and even death [3]. In general, hyponatraemia is known to be a relatively frequent form of electrolyte disturbance among psychiatric and geriatric patients [4].

Numerous case reports have described a possible association between antidepressants and hyponatraemia, however the evidence concerning this association is still incomplete. From these reports it is suggested that hyponatraemia occurs more frequently with SSRIs than with antidepressants having no or minor influence on the serotonergic system [5, 6]; however, controlled pharmacoepidemiological studies in the literature are rare. Siegler and coworkers found that psychiatric inpatients with hyponatraemia were more frequently using fluoxetine than non-recipients with a normal serum-sodium level [7]. Recently, it was found that in daily clinical practise older (≥65 years) psychiatric in- and outpatients using SSRIs more frequently developed hyponatraemia than users of other classes of antidepressant drugs [8]. The incidence of SSRI-induced hyponatraemia has been estimated as almost 5 per 1000 patients treated per year [9].

From these rather small studies it remains unanswered whether this high risk for developing hyponatraemia is specific for one typical antidepressant drug or is an effect common to the class of serotonergic acting antidepressants. The objectives of this study were to determine (a) the relationship between the use of serotonergic antidepressant drugs and the occurrence of hyponatraemia requiring hospitalisation for treatment compared with non-users of these agents and (b) the time-to-admission rate after initiation of a serotonergic antidepressant.

Methods

Data source

The present study was performed with data from the PHARMO record linkage system, a database that includes complete information of hospital admissions and drug-dispensing records from 320,000 inhabitants of eight cities in The Netherlands. This database has been described in detail elsewhere [10]. In brief, complete drug-dispensing records are obtained from pharmacy files and were linked nationwide to the patient's hospital discharge records with a linkage sensitivity and specificity of more than 95%. All drug use is coded according to the Anatomical Therapeutic Chemical classification index of the World Health Organization. Hospital discharge records are coded according to the International Classification of Diseases (ICD-10). For this study drug-dispensing histories and hospital data were collected from January 1990 until December 1998.

Design and patients

In order to determine the risk for hyponatraemia as an adverse reaction to antidepressant drug use a matched case-control study was conducted. Patients aged 18 years and older admitted to a participating hospital with primary or secondary diagnosis of hyponatraemia (ICD-10 code 276.1) or the syndrome of the inappropriate antidiuretic hormone secretion (SIADH, ICD-10 code 253.6) were identified during the study period and were potentially appropriate as case patients. All cases were assigned an index date, which was the date of admission. Three matched community-control patients were sampled from patients who had no hyponatraemia, hypernatraemia (ICD-10 code 276.0) nor SIADH. Cases and controls were matched on year of birth, gender and residential area to take into account possible regional drug-prescribing differences.

Exposure definition

Patients were defined as current drug users if the prescription lasted until the index date. A sensitivity analysis using a 30-day time window prior to the index date was performed for antidepressant drug use; this did not change the number of exposed patients. The first prescription of a drug was defined as a prescription of an agent during the study period and no prescription of the same drug during the 4 months before dispensing. Theoretic duration of exposure was calculated using information on dispensing data, total supply and dosage regimen. From all patients at least 90 days of follow up before the index date was required for inclusion in the study.

Antidepressant drugs were classified into two groups. The first group consisted of antidepressants mainly acting on the serotonergic system (serotonergic antidepressants), which included clomipramine, fluoxetine, fluvoxamine, paroxetine, sertraline and venlafaxine. The second group consisted of non-selective serotonergic-acting antidepressants, which included amitriptyline, imipramine and maprotiline. Clomipramine and venlafaxine were both included in the first group because both are known to be potent antagonists of the serotonin-reuptake mechanism [11]. The time-to-admission rate of hyponatraemia was calculated as the time between the index date and date of initial prescription of an antidepressant.

Potential confounding factors

In order to adjust for factors that may confound the association between antidepressant drug use and the occurrence of hyponatraemia, the following covariates were studied as potential confounders: current use of diuretics, angiotensin-converting enzyme (ACE) inhibitors, calcium-entry blockers, nitrates, beta-blockers, peptic ulcer drugs, antipsychotics, benzodiazepines, anti-epileptics and non-steroidal anti-inflammatory drugs. To define the exposure for concomitantly used medication the same time window as for the antidepressant drugs was used. The following clinical situations were considered also as potential confounders: angina pectoris, diabetes mellitus, heart failure, hepatic diseases, hypertension, lung diseases (lung carcinoma, emphysema), admission myocardial infarction and renal diseases.

Analysis

For both cases and controls the prevalence of each characteristic on the index date was determined. Differences in proportions of categorical variables between cases and controls were tested for significance using 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 (ORs) with 95% confidence intervals (95% CI) were calculated using conditional logistic regression. The final logistic regression model included all univariately associated (at $P \leq 0.1$) risk factors for hyponatraemia.

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. The percentage of hospital admissions for hyponatraemia in the total population that might be explained by serotonergic antidepressant drug use was calculated as the population attributable risk percentage, using the following formula [12]:

$$PAR = \frac{p(OR-1)}{p(OR-1)+1}$$

where p is defined as the population exposure prevalence of serotonergic drug use and OR the odds ratio for admission for hyponatraemia caused by serotonergic antidepressants. All statistical calculations were carried out with the SPSS (version 10.0) and EGRET (version 2.0.3) statistical packages.

Results

Two hundred and eighty-two potential cases of hyponatraemia were identified. Two hundred and three patients (≥18 years old) were confirmed as cases hospitalised due to hyponatraemia and were included in the study. Reasons for exclusion were no drug-use information within the previous 3 months before the index date, discrimination by the age criteria and for one case no controls could be found. Six hundred and eight control patients were matched to the case patients; one case could be matched with only two controls.

Table 1 details demographic and medical characteristics of the study population. Seventy-three percent of the patients were women; the mean age (±SD) was 71 ± 15 years. Baseline exposure to antidepressant drugs was ascertained in 15 cases (7%) and 18 control patients (3%). Of the cases, ten patients (5%) were defined as being exposed to serotonergic antidepressants and 5 patients (2%) to tricyclic antidepressants, compared with non-use resulting in a crude OR of 3.92 (95% CI 1.54, 9.99) and 1.90 (95% CI 0.63, 5.76), respectively.

Further univariate analysis showed that use of ACE inhibitors, antiepileptic drugs, benzodiazepines, beta-blockers, diuretics, peptic ulcer drugs, and four clinical conditions were associated with hyponatraemia. Of the cases using antiepileptics seven of nine were identified as users of carbamazepine, compared with six of 12 of the controls, respectively. These potential confounding factors were adjusted for in the multivariate conditional logistic regression model. It was not possible to estimate a relative risk for lung carcinoma because no controls were classified as cancer patient. Eleven (5%) cases were known with this type of cancer, however, only one case patient used an antidepressant drug. The most frequently used antidepressants were amitriptyline, clomipramine and paroxetine (Table 2).

Table 3 provides the adjusted relative risks for hyponatraemia. Compared with non-recipients of antidepressants the adjusted OR for hyponatraemia associated with current use of antidepressants was 3.96 (95% CI 1.33, 11.83) for serotonergic antidepressants and 1.87 (0.56, 6.24) for non-serotonergic antidepressants. The overall adjusted OR for antidepressant use was 2.75 (95% CI 1.18, 6.45) compared with non-use of antidepressants.

Of the potentially confounding variables, only use of diuretics and peptic ulcer drugs, and the two clinical conditions heart failure and hypothyroidism, remained statistically significantly associated with hyponatraemia. A more detailed analysis showed that patients using

Table 1. Demographic and medical characteristics of cases and controls on the index date. Included are crude odds ratios with 95% confidence intervals (95% CIs). Ratios in bold are included in the multivariate model. *ACE* angiotensin-converting enzyme

	No (%) of cases ($n = 203$)	No (%) of controls ($n = 608$)	Odds ratio (95% CI)
Age, years (mean ± SD)	71 ± 15	71 ± 15	
≥65 years	152 (75)	455 (75)	
< 65 years	51 (25)	153 (25)	
Gender			
Male	54 (27)	162 (27)	
Female	149 (73)	446 (73)	
Antidepressant drugs			
All antidepressants	15 (7)	18 (3)	**2.79 (1.33, 5.85)**
Serotonergic antidepressants	10 (5)	8 (1)	**3.92 (1.54, 9.99)**
Non-serotonergic tricyclic antidepressant	5 (2)	9 (1)	1.90 (0.63, 5.76)
Other	0 (0)	1 (<1)	Not estimable
Concomitant medication			
ACE inhibitors	34 (17)	53 (9)	**2.13 (1.33, 3.40)**
Analgesics	94 (46)	276 (45)	1.04 (0.75, 1.43)
Antiepileptic drugs	9 (4)	12 (2)	**2.25 (0.95, 5.34)**
Antipsychotic drugs	7 (3)	14 (2)	1.52 (0.60, 3.84)
Benzodiazepines	82 (40)	178 (29)	**1.74 (1.22, 2.48)**
Beta-blockers	51 (25)	98 (16)	**1.79 (1.21, 2.66)**
Calcium-entry blockers	25 (12)	53 (9)	1.50 (0.89, 2.51)
Diuretics	101 (50)	156 (26)	**3.38 (1.33, 3.40)**
Nitrates	25 (12)	32 (4)	1.35 (0.80, 2.30)
Peptic ulcer drugs	42 (21)	62 (10)	**2.44 (1.56, 3.84)**
Comorbidity[a]			
Diabetes mellitus	28 (14)	56 (9)	**1.58 (0.97, 2.56)**
Lung cancer	11 (5)	0 (0)	Not estimable
Emphysema	3 (1)	2 (0.3)	**7.24 (0.73, 72.0)**
Heart failure	3 (15)	24 (4)	**4.46 (2.47, 8.05)**
Myocardial infarction	3 (1)	14 (2)	0.63 (0.18, 2.25)
Angina pectoris	2 (1)	16 (3)	0.38 (0.09, 1.63)
Hypothyroidism	6 (3)	1 (0.2)	**18.00 (2.17, 149)**

[a]No other nephrotic, hepatic or endocrine diseases related with hyponatraemia were diagnosed in either cases or controls

Table 2. Distribution of antidepressant drug use on the index date for both cases and controls

Antidepressant	Case ($n=15$)	Control ($n=18$)	Total (33)
Serotonergic antidepressants			
Clomipramine	2	4	6
Fluoxetine	1	0	1
Fluvoxamine	2	1	3
Paroxetine	3	3	6
Sertraline	1	0	1
Venlafaxine	1	0	1
Non-serotonergic tricyclic antidepressants			
Amitryptiine	3	6	9
Imipramine	1	1	2
Maprotiline	1	2	3
Other antidepressant			
Mianserine	0	1	1

thiazides or proton-pump inhibitors had an adjusted 3.21-fold (95%CI 1.68, 6.15) and 2.25-fold (95%CI 1.01, 5.33) higher risk for developing hyponatraemia, respectively. No statistically significant potential interactions between any antidepressant drug and other risk factors were found.

The estimated proportion of serotonergic drug use among controls was 0.013 and the OR for hospital admission because of hyponatraemia caused by serotonergic antidepressants was 3.96. The population-attributable risk percentage was calculated at 0.5%.

For the case patients, the time from starting a serotonergic antidepressant to hospital admission ranged from 1 days to 108 days, with a median time of 10 days. In Fig. 1 is shown that nine of ten cases using these agents were admitted to a hospital within 12 days.

Discussion

In this matched case-control study, we found that patients using serotonergic antidepressants had a fourfold increased risk for hyponatraemia compared with non-recipients of these antidepressant agents. No statistically significant increased risk was found for the group of non-serotonergic antidepressants (tricyclic antidepressants). Our results demonstrate that the risk for hyponatraemia after initiation of a serotonergic antidepressant is highest during the first 2 weeks of drug therapy. Despite the large population studied, it was not possible to estimate relative risks among the individual antidepressant drugs as well as to study a dose-response relationship because of the low number of cases using antidepressants. In a review of 668 spontaneous reported cases of SSRI-induced hyponatraemia no dose-effect relationship was found [13].

In this study other potential risk factors for hyponatraemia were found. Heart failure, hypothyroidism and use of diuretics are widely accepted causes of hyponatraemia [7, 8, 9, 10, 11, 12, 13, 14]. However, peptic ulcer drugs are less well known to induce hyponatraemia [15].

Table 3. Adjusted odds ratios for current risk factors for hospitalisation for hyponatraemia. *ACE* angiotensin-converting enzyme

Antidepressants	Adjusted odds ratio[a]	95% Confidence interval
None	Reference	Reference
Any	2.75	1.18, 6.45
Serotonergic	3.96	1.33, 11.83
Non-serotonergic	1.87	0.56, 6.24
ACE inhibitors	1.10	0.62, 1.95
Antiepileptic drugs	2.11	0.80, 5.59
Benzodiazepines	1.41	0.94, 2.12
Beta-blockers	1.45	0.92, 2.28
Diuretics	2.41	1.59, 3.63
Thiazides	3.21	1.68, 6.16
Loop diuretics	1.71	1.03, 2.83
Peptic ulcer drugs	1.77	1.08, 2.92
Proton pump inhibitors	2.25	1.01, 5.33
H2-antagonists	1.23	0.68, 2.20
Diabetes mellitus	1.41	0.81, 2.44
Heart failure	3.28	1.68, 6.41
Hypothyroidism	18.29	1.96, 171
Emphysema	2.83	0.28, 28.49

[a]Adjusted for each other

The timeframe from start of a serotonergic drug to admission for hyponatraemia shows strong consistency with prior case reviews [5, 6, 16] and earlier studies. In a retrospective study, Strachan and Shepherd [17] found for eight patients, the time from commencement of the SSRI to diagnosing hyponatraemia ranged from 4 days to 28 days (average 12.5 days). Wilkinson and others found a median time of 13.5 days studying 14 patients prospectively [9].

Hyponatraemia is a common finding in psychiatric and geriatric patients. In a healthy elderly population the prevalence of hyponatraemia is estimated to be 5–10%. Bouman and others found a background prevalence of hyponatraemia of 7% in a geriatric psychiatric inpatient population [18]; Miller and co-workers found 11% in an ambulatory geriatric population [19]. Epidemiological data about the incidence of SSRI-induced hyponatraemia is scarce and inconsistent. In two case-note reviews high prevalences of hyponatraemia were found among patients following introduction of a SSRI [17, 18]. However, in one study the incidence for hyponatraemia was estimated as 6.3 per 1000 patients for fluoxetine and 3.5 per 1000 patients for paroxetine [9]. The results from our study are consistent with a previous study, with regard to the fact that serotonergic antidepressants more frequently cause hyponatraemia than non-serotonergic acting agents [8].

Hyponatraemia associated with antidepressants is most probably secondary to SIADH [20]. The exact nature of the biological mechanism is unknown and remains speculative. However in animal studies, a possible stimulating effect of serotonin on antidiuretic hormone secretion seems to be mediated by various subtypes of serotonin receptors.

As with other observational studies, the present study may have been affected by bias or confounding. In general, selection bias is a realistic threat to the validity

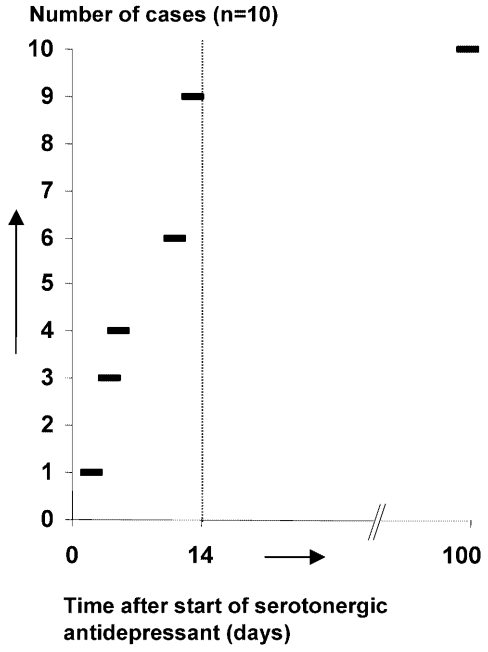

Fig. 1. Time from start of serotonergic antidepressant to onset of hyponatraemia

of a case-control study. The association between serotonergic antidepressants and hyponatraemia could be biased in this sense if these drugs were preferentially prescribed to patients already at an increased risk for hyponatraemia. We therefore tended to correct for several potential confounders in the logistic model. However, none of the other covariates substantially affected the observed risk estimate for hyponatraemia. Of course the possibility still exists for residual confounding as a result of unmeasured or inaccurately measured risk factors such as smoking. We did match for age and gender because these variables are already known to be strong risk factors for hyponatraemia [7, 8]. Selection could also occur if patients using antidepressants are more frequently tested for blood sodium than patients who don't take these agents. Also, the reason for performing blood tests may have been different between the two groups, e.g. they may be done for routine identification of hyponatraemia in SSRI recipients, while they are done more often to investigate physical illness in non-recipients. However, symptoms of hyponatraemia are often non-specific and not always looked for. So, from this point of view only clinically serious cases of hyponatraemia are referred to a hospital and detected by an automated hospital admission database.

Another limitation of this study might be misclassification in the selection of the case patients. We think that diagnostic bias is unlikely because of the seriousness of this clinical event, which is confirmed on laboratory sodium measurements. Previous validation of the database used showed a high sensitivity suggesting a low percentage of misclassification of the primary diagnostic outcome [10]. Prescription data in the PHARMO database is found to have a high standard of data completeness and accuracy, so misclassification of antidepressant use was unlikely.

It is not likely that referral bias has occurred. We believe that the awareness of physicians for the association between serotonergic agents (or any other antidepressant) and hyponatraemia is low. It is most likely that patients with less severe, non-symptomatic hyponatraemia are not admitted to a hospital. In that situation only the severe cases of clinically relevant hyponatraemia are included in our study. However, one can expect more often routine laboratory control measurements among users of non-serotonergic (tricyclic) antidepressants because of the strict need for therapeutic drug monitoring when using these kind of antidepressants.

Despite these limitations, major advantages of this study compared with the previous ones are its large number of hyponatraemic case patients sampled from a 'real-life' population and the possibility to make a direct comparison between users and non-users of antidepressants. As such, the population included is more representative of the general elderly population in daily clinical practise with hyponatraemia than studies using selected cases and controls from only inpatient populations. This study overcomes the methodological problems of Wilkinson's case-control study. In their study it was not possible to estimate a relative risk because both case and control patients used SSRIs [9]. In contrast with Bouman's study [18], in our study it was possible to detect the time course between SSRI initiation and onset of hyponatraemia in a representative population.

In conclusion, use of serotonergic antidepressants is associated with the occurrence of hyponatraemia requiring hospitalisation in an elderly, outpatient population. Hyponatraemia seems to occur mainly during the first weeks of drug treatment. Calculation of the population attributable risk percentage suggests that use of serotonergic antidepressants could explain about 0.5% of all hospital admissions for hyponatraemia. Given that serotonergic antidepressants are increasingly prescribed and the seriousness of hyponatraemia we consider it important to monitor serum-sodium levels regularly in elderly patients, at least during the first period of serotonergic drug use. In daily clinical practise the possibility of hyponatraemia induced by serotonergic antidepressants should be borne in mind by the prescribing physician, and attentiveness is desired for non-specific symptoms possibly indicating low sodium serum levels.

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