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

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
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.

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]:

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P_{\text{AR}} = \frac{p(\text{OR} - 1)}{p(\text{OR} - 1) + 1}
\]

where \( p \) is defined as the population exposure prevalence of serotonergic drug use and \( \text{OR} \) 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.