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Hyponatraemia as an Adverse Drug Reaction of Antipsychotic Drugs

A Case-Control Study in VigiBase

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Abstract

Background: Hyponatraemia due to antipsychotic use is a potentially serious problem; however, it is not known whether it is an adverse drug reaction (ADR) to antipsychotic use or is due to the underlying psychiatric disease.

Objective: To estimate the strength of the association between antipsychotics and hyponatraemia or syndrome of inappropriate antidiuretic hormone secretion (SIADH), using information reported to the WHO Collaborating Centre for International Drug Monitoring, the Uppsala Monitoring Centre (UMC).

Setting: The WHO global individual case safety report database system (VigiBase) maintained by the UMC.

Study Design: Case-control study, with cases being reports of hyponatraemia/SIADH, and controls being reports of other ADRs. Each case was sampled with ten controls sequencing in time from the date the corresponding case was entered into the database. The potential contribution of the chemical structures and receptor affinity (dopaminergic and/or serotonergic) of the antipsychotics was studied, as was the influence of concomitant use of other medications known to cause hyponatraemia.

Main Outcome Measures: The strength of the association between antipsychotic use and hyponatraemia in comparison with other drugs was expressed as reporting odds ratio (ROR), a measure of disproportionality, with corresponding 95% CIs, adjusted for age, sex and concomitant medication associated with hyponatraemia. In addition, stratification by the presence or absence of concomitant medication was performed.

Results: Up to August 2008, 3 881 518 suspected ADRs were reported and filed in VigiBase, with 912 reports on hyponatraemia related to antipsychotics. The adjusted ROR for the association between antipsychotic use and hyponatraemia was 1.58 (95% CI 1.46, 1.70). The adjusted RORs did not vary for the different chemical structures or dopamine D_2 and serotonin 5-HT_{2A} receptor affinity profiles. The ROR was 3.00 (95% CI 2.65, 3.39) for the association between hyponatraemia and antipsychotic use in the absence of concomitant medication associated with hyponatraemia, and 1.16 (95% CI 1.06, 1.28) in the presence of concomitant medication associated with hyponatraemia.

Conclusions: Antipsychotic use may be associated with reporting of hyponatraemia. Moreover, the concomitant use of medication associated with hyponatraemia potentially leads to under-reporting of antipsychotic-associated hyponatraemia. We advise testing patients whose psychiatric and/or physical condition deteriorates while on antipsychotics for hyponatraemia.

Background

Hyponatraemia may have serious clinical consequences, such as delirium, seizures and rhabdomyolysis, and is a risk factor for neuroleptic malignant syndrome,[1] making it a potentially fatal condition.[2] Hyponatraemia occurs in about 4% of patients with schizophrenia[3,4] and occasionally in patients with other psychiatric disorders, such as manic depressive psychosis and psychotic depression.[5]

Hyponatraemia may be due to the chronic psychiatric disorder itself.[6] In psychiatric patients, psychogenic polydipsia and the syndrome of inappropriate antidiuretic hormone secretion (SIADH) may cause hyponatraemia. A subset of patients with schizophrenia experience psychosis intermittent hyponatraemia and polydipsia (PIP) syndrome.[7,8] It has been suggested that polydipsia in itself is not sufficient to cause hyponatraemia because the kidneys are able to produce a great amount of maximally diluted urine, and thus other factors must be present for hyponatraemia to occur. These factors could include increased levels of antidiuretic hormone (ADH) as a result of stress, pain, drugs, SIADH[9-11] or an impaired ability of the kidney to concentrate urine.[12] In patients with or without polydipsia, the hyponatraemia can be caused by dysregulation of ADH, as in SIADH or 'reset osmostat' (a condition in which ADH concentrations are high relative to osmolality). The latter was found in a subset of schizophrenic patients with polydipsia.[13-15]

Hyponatraemia may also be an adverse drug reaction (ADR). Although published case reports suggest an association between antipsychotics and hyponatraemia,[2,10,11,16-25] the causality of this relationship has been questioned.[5,26] However, in a recent review of case reports from the literature, we found an association between hyponatraemia and the use of antipsychotic drugs.[25] Based on these case reports, the incidence cannot be established. If this possible ADR occurs in daily practice and is subsequently reported to pharmacovigilance centres, this provides an impression that this ADR is considered relevant in daily practice.

The objective of this study is to look for a relationship between the reporting of hyponatraemia and the use of antipsychotics in the WHO database for individual case safety reports (ICSRs) of ADRs (VigiBase) and, if there is a relationship, to establish whether the chemical structure or dopamine D_2 and serotonin 5-HT_{2A} receptor affinity profiles of antipsychotics influences this.[27-29] A secondary objective was to study whether the use of medications known to

be associated with hyponatraemia and SIADH (other than antipsychotic drugs) influences the reporting of hyponatraemia among patients taking antipsychotics.

Methods

Setting

The Uppsala Monitoring Centre (UMC) maintains VigiBase on behalf of the WHO.[30] Currently more than 4.6 million ADR reports from more than 90 countries are filed in the database.[31] One of the objectives of the UMC is to collect, record and analyse data on reported ADRs. At a national level, ADRs are reported by healthcare professionals and in some countries by patients or pharmaceutical companies. Reports include patient demographic characteristics (such as age and sex), the suspected medication, concomitant medication, one or more reported ADRs and relevant clinical information. These reports are forwarded by the various national centres to the UMC. The VigiBase data are heterogeneous, at least with respect to origin (country as well as reporter of the ADR) and content (e.g. quality and assessment of causality).[31] ADRs are coded according to the WHO Adverse Drug Reaction Terminology (WHO-ART) or the Medical Dictionary for Regulatory Activities (MedDRA®).[31] The suspected drugs are classified according to the WHO Drug Dictionary. For the current study, the WHO Anatomical Therapeutic Chemical (ATC) classification system, which is linked to the WHO Drug Dictionary, was used.

Selection of Cases and Controls

Cases were defined as all reports containing an ADR coded with the WHO-ART preferred term hyponatraemia or SIADH. Each case was sampled with ten controls sequencing in time from the date the report of the corresponding case was entered into VigiBase. Since reports are filed in the database by batch from one country at a time, controls were not only matched in time, but also for country of origin.

Cases and controls with no information on age or sex were excluded. This was done as the final step in the preparation of the dataset. Cases and controls were not matched for age and sex, but these were analysed as co-variates.

Exposure Definition

The index group consisted of reports in which the reporter suspected that a prescribed antipsychotic (classified according to ATC code beginning with N05A excluding lithium N05AN) was a causal factor in the development of hyponatraemia. Antipsychotics mentioned more than five times were classified by chemical class,[32] and D_2 and 5-HT_{2A} receptor affinity.[33]

Co-Variates

Age, sex and concomitant medication associated with hyponatraemia in the literature were considered as co-variates. The selection of drugs associated with hyponatraemia was based on an overview article on drug-induced hyponatraemia by Ma et al.[34] (table I). This concomitant medication was not suspected by the reporter as causing the hyponatraemia.

Data Analysis

For cases and controls, the number and percentage of antipsychotic users, mean age with standard deviation, number and proportion of females, and numbers of users of concomitant medication associated with hyponatraemia were

Table I. Drugs associated with hyponatraemia[34]

Category	Associated medication
CNS	Benzodiazepines, antidepressants, valproate, carbamazepine, oxcarbazepine, phenytoin, NSAIDs, opioids
Cardiovascular system	Diuretics, β-blockers, ACE inhibitors, nitrates, calcium channel antagonists, amiodarone, clofibrate
Endocrine	Chlorpropamide, sulphonylurea, biguanides, thiazolidinediones, vasopressin, desmopressin, bromocriptine
Cytotoxic drugs	Cyclophosphamide, vinblastine, vincristine, cisplatin

Table II. Characteristics of cases and controls

Characteristic	Cases (n = 15 728)	Controls (n = 129 525)	p-Value
Users of antipsychotic drugs [n (%)]	912 (5.8)	6 916 (5.3)	p < 0.0001 (Pearson Chi-square test)
Mean age [y (SD)]	66.5 (18.5)	51.8 (21.4)	p < 0.0001 (Student's t-test)
Sex, females [n (%)]	10 459 (66.5)	73 997 (57.1)	p < 0.0001 (Pearson Chi-square test)
Concomitant use of medication associated with hyponatraemia [n (%)][a]	12 491 (79.4)	58 163 (44.9)	p < 0.0001 (Pearson Chi-square test)

a List of included medications can be found in table I.

calculated. In order to calculate differences in age between cases and controls, the Student's t-test was used. In order to calculate differences in sex and the presence of concomitant medication associated with hyponatraemia, the Pearson Chi-square test was used.

The strength of the association between antipsychotic use and hyponatraemia in comparison with the use of other drugs is expressed as reporting odds ratio (ROR), a measure of disproportionality, with corresponding 95% CIs.[35,36] The ROR provides an estimate of the extent to which hyponatraemia is reported in association with an antipsychotic as suspected medication relative to reports of hyponatraemia in patients using other drugs. The ROR was calculated by dividing the numerator (the number of cases with an antipsychotic as the suspected medication divided by the number of cases with another suspected drug) by the denominator (the number of controls with an antipsychotic as the suspected drug divided by the number of controls with another suspected drug). The ROR was adjusted for age, sex and concomitant medication associated with hyponatraemia. The crude RORs and adjusted RORs were estimated by means of logistic regression analysis separately for antipsychotic class (typical and atypical antipsychotics), chemical structure and pharmacological characteristics, and for the various individual antipsychotics. Statistical analysis was conducted using the software package SPSS 16.0 for Windows (SPSS, Chicago, IL, USA).

Results

VigiBase contained 3 881 518 reports filed up to August 2008, with 15 728 (0.4%) reports of hyponatraemia (cases) with data on age and sex. These cases were matched with 129 525 controls. Since exclusion of cases and controls with no information on age or sex was done as the final step in the preparation of the dataset, the actual number of controls per case was not 10 but 8.23. Compared with the controls, the cases were older (mean age 66.5 vs 51.8 years; $p < 0.0001$) and more often female (66.5% vs 57.1%; $p < 0.0001$). Concomitant medication associated with hyponatraemia was used in 79.4% of the cases and in 44.9% of the controls ($p < 0.0001$) [table II]. Of the cases, 912 reports (5.8%) mentioned an antipsychotic as suspected medication compared with 6916 (5.3%) among the controls (adjusted ROR 1.58 [95% CI 1.46, 1.71]).

Atypical psychotics were used in 631 cases, and typical antipsychotics were used in 274 cases (because we only included antipsychotics that had been reported five times or more to be a suspected cause of hyponatraemia, the number of cases involving typical and atypical antipsychotics was less than the total number of cases using antipsychotics), with risperidone (n = 198 cases), olanzapine (n = 168 cases) and clozapine (n = 141 cases) being the antipsychotics mentioned most often in association with hyponatraemia. Adjusted RORs for hyponatraemia were 1.66 (95% CI 1.45, 1.91) for typical antipsychotics (see table III) and 1.55 (95% CI 1.41, 1.69) for atypical antipsychotics (table IV). For the individual antipsychotics, the highest adjusted ROR was for fluphenazine (6.91 [95% CI 4.45, 10.73]) and the lowest was for cyamemazine (0.77 [95% CI 0.45, 1.31]).

There was no association between chemical structure and D_2 and 5-HT_{2A} receptor affinity (table V) and reports of hyponatraemia.

Stratification by the concomitant use of medication associated with hyponatraemia showed

that the association between antipsychotic use and reports of hyponatraemia was significantly higher in the absence of concomitant use of such medication (table VI). The adjusted ROR was 1.16 (95% CI 1.06, 1.28) for concomitant use of medication associated with reports of hyponatraemia/SIADH and 3.00 (95% CI 2.65, 3.39) without concomitant use of such medication.

Discussion

This study showed that antipsychotic use is associated with reporting of hyponatraemia in VigiBase. This association was statistically comparable for typical and atypical antipsychotics and did not statistically differ by chemical class or affinity for D_2 and 5-HT_{2A} receptors. Most reports concerned the newer atypical antipsychotics, especially risperidone, olanzapine and clozapine. Reporting of ADRs tends to be higher for newly marketed drugs and declines with time,[37] which may explain the high number of ADR reports for these drugs. The association between antipsychotics and reports of hyponatraemia was stronger in those cases in which patients did not use concomitant medication associated with hyponatraemia. Selective reporting may cause this difference: clinicians reporting hyponatraemia as an ADR might consider the concomitant medication associated with hyponatraemia to be responsible and thus less frequently ascribe hyponatraemia to the antipsychotic used. As reported in the literature, most cases of hyponatraemia involved older individuals[38-40] and women.[41]

Clinicians are probably aware of antipsychotic-induced hyponatraemia because several case reports have been published.[25] The results from this study on voluntary reports of ADRs support this; however, spontaneous reporting systems are subject to various types of bias, confounding and misclassification. Neither the incidence nor the prevalence of this ADR can be calculated based on this dataset.

Interestingly, some atypical antipsychotics are reported to have a beneficial effect on polydipsia

Table III. Crude and adjusted reporting odds ratios (RORs) for the association between typical antipsychotics, grouped by chemical class,[32] and affinity for dopamine D_2 and serotonin 5-HT_{2A} receptors[33] and hyponatraemia

Pharmacological classification	Receptor affinity strong		Cases (n)	Crude ROR (95% CI)	Adjusted ROR (95% CI)[a]
	D_2	5-HT_{2A}			
Total			274[b]	1.45 (1.28, 1.65)	1.66 (1.45, 1.91)
Phenothiazines			134	1.29 (1.06, 1.56)	1.98 (1.63, 2.41)
fluphenazine	Yes	Yes	31	3.24 (2.14, 4.90)	6.91 (4.45, 10.73)
trifluoperazine	Yes	No	12	1.57 (0.85, 2.91)	2.24 (1.16, 4.31)
thioridazine	Yes	Yes	32	1.72 (1.18, 2.52)	1.93 (1.28, 2.90)
levomepromazine	No	No	23	1.40 (0.90, 2.19)	1.68 (1.06, 2.68)
prochlorperazine	No	No	18	0.87 (0.54, 1.42)	1.57 (0.93, 2.65)
chlorpromazine	Yes	Yes	26	0.96 (0.64, 1.44)	1.34 (0.87, 2.05)
Butyrophenones			114	1.46 (1.18, 1.80)	1.81 (1.46, 2.25)
haloperidol	Yes	No	107	1.58 (1.28, 1.94)	1.85 (1.48, 2.31)
pipamperone	No	No	7	1.38 (0.62, 3.06)	1.28 (0.54, 3.07)
Thioxanthenes			28	1.54 (1.02, 2.35)	2.76 (1.78, 4.25)
flupenthixol	Yes	No	17	2.06 (1.21, 3.51)	3.65 (2.05, 6.50)
zuclopenthixol	Yes	No	11	1.21 (0.64, 2.28)	2.00 (1.03, 3.89)
Benzamides					
tiapride	No	No	14	1.42 (0.81, 2.51)	0.89 (0.49, 1.62)

a Adjusted for age, sex and concomitant medication.

b A report may contain more than one suspected antipsychotic drug. For this reason, the total number of reports in which an individual typical antipsychotic drug (n = 290) was mentioned as the suspected drug was higher than the total number of reports in which a typical antipsychotic drug was mentioned as the suspected drug (n = 274).

Table IV. Crude and adjusted reporting odds ratios (RORs) for the association between atypical antipsychotics and hyponatraemia stratified by affinity for dopamine D_2 and serotonin 5-HT_{2A} receptors[33]

Atypical antipsychotic drug	Receptor affinity strong		Cases (n)	Crude ROR (95% CI)	Adjusted ROR (95% CI)[a]
	D_2	5-HT_{2A}			
Total			631[b]	0.99 (0.91, 1.08)	1.55 (1.41, 1.69)
Ziprasidone	Yes	Yes	23	1.71 (1.09, 2.67)	2.81 (1.74, 4.56)
Risperidone	Yes	Yes	198	1.52 (1.30, 1.77)	2.27 (1.93, 2.68)
Olanzapine	No	Yes	168	1.45 (1.23, 1.71)	2.14 (1.80, 2.55)
Sulpiride	No	No	24	2.20 (1.40, 3.45)	1.99 (1.22, 3.21)
Amisulpiride	Yes	Yes	19	1.24 (0.77, 2.01)	1.93 (1.14, 3.24)
Aripiprazole	Yes	Yes	15	0.78 (0.46, 1.32)	1.50 (0.86, 2.62)
Quetiapine	No	No	38	0.95 (0.68, 1.34)	1.34 (0.94, 1.91)
Clozapine	No	Yes	141	0.52 (0.44, 0.61)	1.22 (1.02, 1.46)
Loxapine	Yes	Yes	7	0.62 (0.29, 1.34)	0.78 (0.35, 1.73)
Cyamemazine	Yes	Yes	16	0.72 (0.43, 1.20)	0.77 (0.45, 1.31)

a Adjusted for age, sex and concomitant medication.

b A report may contain more than one suspected antipsychotic drug. For this reason, the total number of reports in which an individual atypical antipsychotic drug (n = 649) was mentioned as the suspected drug was higher than the total number of reports in which an atypical antipsychotic drug was mentioned as the suspected drug (n = 631).

and hyponatraemia in schizophrenic patients, as reported in prospective studies for clozapine.[42-45] This has also been described in case reports for olanzapine,[46,47] risperidone[48,49] and quetiapine.[49,50] More detailed studies, preferably randomized controlled trials, are needed on this issue.

The mechanism by which antipsychotic drugs induce hyponatraemia is still unclear. It is generally thought that antipsychotics (both typical and atypical) stimulate ADH release in the brain[51,52] and/or enhancement of the activity of ADH on the kidney,[6] although it has also been suggested that both typical[53-60] and atypical[48] antipsychotics induce severe polydipsia by stimulating the thirst centre or by causing a dry mouth.[61]

The list of concomitant medications associated with hyponatraemia used in this study was based on a review published in 2007,[62] the most current at the time the data were extracted from VigiBase. The association of these drugs with hyponatraemia/SIADH was established at the time of data extraction. In a more recent review published in 2008,[63] other drugs used in everyday clinical practice (e.g. newer antihypertensive agents, antibacterials, proton pump inhibitors) have become implicated as a possible cause of hyponatraemia and should be considered for inclusion in future studies.

The use of VigiBase has implicit limitations because the incidence of ADR reporting is influenced by various factors.[64] New antipsychotic drugs are introduced at different times in

Table V. Crude and adjusted reporting odds ratios (RORs) for antipsychotics and their affinity for dopamine D_2 and serotonin 5-HT_{2A} receptors

Antipsychotic drug	No. of cases with hyponatraemia	Crude ROR (95% CI)	Adjusted ROR (95% CI)[a]
Antipsychotic drugs with strong D_2 receptor affinity	495	1.41 (1.28, 1.56)	1.77 (1.59, 1.97)
Antipsychotic drugs without strong D_2 receptor affinity	417	0.83 (0.75, 0.92)	1.47 (1.32, 1.64)
Antipsychotic drugs with strong 5-HT_{2A} receptor affinity	641	1.02 (0.94, 1.10)	1.61 (1.59, 1.97)
Antipsychotic drugs without strong 5-HT_{2A} receptor affinity	271	1.27 (1.12, 1.44)	1.40 (1.22, 1.61)

a Adjusted for age, sex and concomitant medication.

Table VI. Crude and adjusted reporting odds ratios (RORs) in antipsychotic users with hyponatraemia, stratified by concomitant use of medication associated with hyponatraemia

Concomitant medication	No. of reports [n (%)]	Crude ROR (95% CI)	Adjusted ROR (95% CI)[a]
No concomitant medication associated with hyponatraemia	70 654 (48.6)	2.11 (1.88, 2.37)	3.00 (2.65, 3.39)
Concomitant medication associated with hyponatraemia	74 599 (51.4)	0.83 (0.76, 0.91)	1.16 (1.06, 1.28)

a Adjusted for age and sex.

different countries, making it possible for selection bias to be present.[37] Notoriety bias, entailing media (both scientific and general) attention on certain adverse effects of medication, might influence the reporting of ADRs over time.[65,66] Because cases were sampled with controls in time sequence (the date of the report of the corresponding case was entered into VigiBase and these reports were filed in the database by batch one country at a time), selective bias based on different reporting rates over time in various countries is less likely to have influenced the results. Also, selection bias, like under-reporting, notoriety bias[65,66] and the Weber effect,[37] does not necessarily influence the magnitude of the ROR, although the extent of selection bias cannot be estimated.[67] Non-elective under- and over-reporting of the drug or ADR does not have an influence on the ROR, since nominator and denominator are both influenced in the same way, whereas selective under-reporting, i.e. specific reporting of a combination of drug and ADR, do have an influence on the ROR.

Reports with missing information on age and sex were excluded after matching cases and controls. It appears that the final number of controls per case was 8.2, which is lower than the number of controls per case that we initially intended. To rule out the theoretical possibility of selection bias, we calculated the crude RORs before and after the exclusion of cases and controls with missing information on age and/or sex. In both situations, the adjusted ROR for antipsychotic use and reporting of hyponatraemia was 1.58 (95% CI 1.46, 1.70). The crude RORs were almost the same: 1.13 (95% CI 1.06, 1.20) including the cases and controls with the missing information on age and sex, and 1.09 (95% CI 1.02, 1.17) in the cases and controls with complete information on these co-variates. In both situations, the ROR adjusted for the use of concomitant medication was 1.58 (95% CI 1.46, 1.70). Selection bias due to the exclusion of these cases is therefore unlikely.

Another form of selection bias that may be involved is protopathic bias.[68] Hyponatraemia due to other causes may lead to psychiatric symptoms, such as delirium. This may prompt the prescription of antipsychotics without further investigation of other potential causes of the symptoms, such as hyponatraemia. When hyponatraemia is detected during antipsychotic treatment in these patients, it may erroneously be considered an ADR of the antipsychotic drug and lead to over-reporting. Protopathic bias can have influenced the results, certainly in settings with difficult access to laboratorial measurements. Confounding by indication could also have influenced the results. Psychiatric diseases themselves may be associated with hyponatraemia due to SIADH and polydipsia,[6] but are also a reason to prescribe antipsychotic drugs. Thus, clinicians may erroneously conclude that hyponatraemia is the result of the ADR and not the result of the underlying psychiatric disease. Data on the indication for the antipsychotic drug in the reports of VigiBase are incomplete, making it impossible to adjust for confounding by indication.

Insufficient data are present in the reports in VigiBase to make a correct diagnosis of SIADH, a diagnosis already difficult to make in daily practice.[69] It cannot be ruled out that in clinical practice misclassification may occur, which was our reason for analysing hyponatraemia and SIADH together. More detailed studies are needed to look into the nature of hyponatraemia in patients using antipsychotics.

The primary goal of VigiBase is to signal the existence of a possible relationship between a drug or drugs and an ADR. We found antipsychotic use to be associated with the reporting

of hyponatraemia, but many aspects may influence reporting of ADRs. Although the finding of this study corroborates previous reports in the literature of a possible association between the use of antipsychotics and the occurrence of hyponatraemia, an estimation of the incidence of this ADR cannot be made based on these data.

Conclusions

Antipsychotic use was found to be associated with reporting of hyponatraemia as a possible ADR in VigiBase. Moreover, the concomitant use of drugs known to give rise to hyponatraemia appears to be a cause of selective under-reporting. We hope that our findings raise awareness of the possibility of hyponatraemia developing in patients treated with antipsychotics and recommend testing for hyponatraemia in patients whose psychiatric or physical condition deteriorates while taking antipsychotics.

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