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Case Report

Psychiatry/Mental Health Section

Low-dose Mirtazapine Induced Hyponatraemia with Probable Syndrome of Inappropriate Antidiuretic Hormone Secretion in an Elderly Male: A Case Report

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ABSTRACT

Hyponatraemia is a common and potentially serious condition in elderly patients. It is associated with significant morbidity including delirium, falls and prolonged hospitalisation. Antidepressant induced hyponatraemia is a recognised adverse effect, most commonly attributed to Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH). Although Mirtazapine is often considered a safer alternative to other antidepressant-induced hyponatraemia, reports of SIADH related to its use remain limited. We report the case of a 72-year-old male with dementia and Behavioural and Psychological Symptoms of Dementia (BPSD) who developed symptomatic hyponatraemia 15 days after initiation of mirtazapine (3.75 mg/day). Evaluation revealed hypotonic hyponatraemia with a serum sodium level of 122 mEq/L, serum osmolality of 253 mOsm/kg, urine spot sodium of 31.1 mEq/L and clinical euvolaemia. Alternative causes of hyponatraemia and SIADH including adrenal insufficiency, hypothyroidism, renal dysfunction, cardiac failure, malignancy, respiratory disease, HIV infection and acute intracranial pathology were excluded. Mirtazapine was stopped while concomitant medications were continued unchanged along with fluid restriction and high-salt diet which resulted in improvement of serum sodium levels and resolution of hyponatraemia associated delirium within three days. The likelihood of Mirtazapine use causing hyponatraemia was probable (score 7) as per the Naranjo Adverse drug reaction probability scale. This case describes probable mirtazapine-associated SIADH occurring at a low dose of 3.75 mg/day in an elderly male and highlights the importance of baseline evaluation and regular monitoring of serum sodium along with vigilance for clinical signs of hyponatraemia in elderly patients and those with risk factors receiving mirtazapine although mirtazapine is considered a safer alternative for other antidepressant-induced hyponatraemia.

Keywords: Aged, Antidepressive agents, Drug-related side-effects and adverse reactions, Geriatric psychiatry, Water-electrolyte imbalance

CASE REPORT

A 72-year-old male from a middle socioeconomic background residing in a semi-urban area, with good social support presented to the psychiatry outpatient department with worsening Behavioural and Psychological Symptoms of Dementia (BPSD) with low mood and sleep disturbances over the past two weeks. The patient was a known case of dementia with BPSD for two years. In view of worsening BPSD the patient was admitted in the psychiatry ward requiring symptomatic management and a plan was made to initiate cognitive stimulation therapy and behavioural management. The patient is on treatment with Memantine 5 mg once a day for dementia with BPSD. The patient had previously been diagnosed with F03 (unspecified dementia) and F06.8 (other specified mental disorders due to brain disease), according to the International Classification of Diseases, 10th Revision (ICD-10) [1]. The patient had type 2 diabetes mellitus, for which he was receiving metformin 500 mg once daily; systemic hypertension, treated with amlodipine 5 mg once daily; coronary artery disease, managed with clopidogrel 75 mg/atorvastatin 10 mg once daily at bedtime; and Parkinson's disease, treated with a fixed-dose combination of levodopa 100 mg and carbidopa 25 mg twice daily. The patient was on regular treatment for all the above mentioned medical conditions. During admission, mirtazapine was initiated at a dose of 3.75 mg/day to address low mood and sleep disturbances.

The patient was moderately built. Baseline serum sodium prior to initiation of mirtazapine was 134 mEq/L. After 15 days of mirtazapine use, the patient developed acute onset confusion and restlessness with fluctuating sensorium. Assessment using the Confusion Assessment Method for the ICU (CAM-ICU) confirmed the presence of delirium [2]. Laboratory investigations revealed serum sodium 122 mEq/L, blood urea nitrogen 8 mg/dL and serum creatinine 0.6 mg/dL. Spot urine sodium was 31.1 mEq/L, serum osmolality was 253 mOsm/kg, and serum uric acid was 2.5 mg/dL. Random blood sugar, serum cortisol, thyroid function tests, liver function tests and complete blood count were within normal limits. Two-dimensional echocardiography and chest radiography revealed no significant abnormalities. Clinically, the patient was euvolaemic, with no signs of dehydration, normal peripheral pulses, normal pulse rate and blood pressure and normal skin turgor. The patient was not receiving any antidepressants prior to admission and was not on diuretics or any other medications known to cause hyponatraemia. MRI brain showed diffuse cerebral cortical atrophy with no evidence of acute infarction, intracranial haemorrhage, space occupying lesions or other acute intracranial pathology thereby excluding an acute structural intracranial cause of delirium. No other causes of hyponatraemia or Syndrome of Inappropriate Antidiuretic Hormone secretion (SIADH) including tumours, respiratory system disease or HIV infection were identified. Mirtazapine was discontinued. The patient had hypotonic hyponatraemia with serum sodium of 122 mEq/L, serum osmolality of 253 mOsm/kg with clinical euvolaemia, elevated urinary sodium levels of 31.1 mEq/L, and normal thyroid, cardiac and adrenal function, findings consistent with the diagnostic framework proposed by Schwartz and Bartter for SIADH [3]. Alternative causes of hyponatraemia including adrenal insufficiency,

hypothyroidism, renal dysfunction, cardiac failure, tumours, respiratory disease, HIV infection and acute intracranial pathology were evaluated and excluded as detailed above and a clear temporal relationship was observed between the initiation of mirtazapine and the onset of hyponatraemia. The patient was advised fluid restriction and a high-salt diet. After three days of discontinuing mirtazapine, the confusion and restlessness has resolved without the need for additional correction and serum sodium has improved to 133 mEq/L.

DISCUSSION

Hyponatraemia is one of the most common fluid and electrolyte imbalances in hospitalised patients and occurs more frequently among the elderly [4]. It is a potentially serious condition especially in elderly patients when presenting with delirium. A systematic review has reported that mirtazapine induced hyponatraemia is relatively uncommon, with an incidence of 3.26%, most commonly attributed to SIADH [5].

The present case describes the development of probable mirtazapine-associated SIADH in a 72-year-old male with dementia and BPSD, manifesting as symptomatic hyponatraemia with a serum sodium nadir of 122 mEq/L within 15 days of initiating mirtazapine at a low dose of 3.75 mg/day. The likelihood of Mirtazapine use causing hyponatraemia in this case was probable (score 7) according to the Naranjo Adverse Drug Reaction Probability Scale [6].

As per the systematic review which included seven cases, the mean dose was 19.28 mg/day (7.5 mg-30 mg), however in the index case it was only 3.75 mg/day even though the mirtazapine induced hyponatraemia is dose independent [5]. In the systematic review mentioned above , Ladino M et al., reported mirtazapine-associated hyponatraemia in a 72-year-old male receiving 7.5 mg/day, with a serum sodium nadir of 116 mEq/L occurring within six days of initiation [7], while Cheah CY et al., reported profound hyponatraemia in a 61-year-old male and a 79-year-old female receiving 15 mg/day and 30 mg/day, respectively, with serum sodium nadirs of 112 and 113 mEq/L occurring within seven and ten days of treatment initiation, notably, both these patients were receiving concomitant diuretic therapy, a recognised risk factor for hyponatraemia [8]. Ghosh A et al., reported hyponatraemia in a 46-year-old female following an increase in mirtazapine dose from 15 mg/day to 22.5 mg/day [9]. Compared with these reports, the present patient developed symptomatic hyponatraemia with a serum sodium nadir of 122 mEq/L at a very low dose of 3.75 mg/day making it clinically noteworthy [5]. In the index case the hyponatraemia had occurred after 15 days of mirtazapine use like some studies where antidepressant induced hyponatraemia occurs within a month approximately [5,10]. According to a meta-analysis [11], mirtazapine has the lowest risk of hyponatraemia among antidepressants. Consequently, mirtazapine is often considered a safer alternative in patients with other antidepressant induced hyponatraemia [5,11-13]. Recognised risk factors like concomitant use of other hyponatraemia inducing medications [5,8,14], low body weight and renal dysfunction [15] were not present in the current case. Euvolaemic hyponatraemia may occur secondary to SIADH, adrenal insufficiency, hypothyroidism, primary polydipsia, low-solute intake states and drug-induced causes [16]. Alternative causes of hyponatraemia were systematically considered. Adrenal insufficiency was considered unlikely in view of a normal 8 AM serum cortisol level, hypothyroidism was excluded by normal thyroid function tests and renal dysfunction was ruled out by normal renal function parameters. Clinical examination was consistent with euvolaemia and there were no clinical features suggestive of cardiac failure such as dyspnoea, orthopnoea or pedal oedema, nor was there echocardiographic evidence of cardiac failure. Medication-induced hyponatraemia due to the patient's long-term comorbidity medications was considered less likely because these medications were continued unchanged, whereas mirtazapine was discontinued following which serum sodium levels improved and clinical symptoms resolved. Collectively, these findings support a probable diagnosis of mirtazapine associated SIADH.

Pharmacologically, mirtazapine acts through serotonin receptor blockade (5-HT2A and 5-HT3 receptors), histamine H1 receptor blockade, and alpha-2 adrenergic receptor blockade of both autoreceptors and heteroreceptors in serotonergic neurons, resulting in increased serotonergic and noradrenergic neurotransmission [17]. The development of SIADH may be related to its serotonergic effects, however the exact mechanism of antidepressant induced SIADH remains unclear [10]. In elderly psychiatric patients treated with SSRIs and SNRIs, female sex has been associated with an increased risk of hyponatraemia [18] and Drug-induced hyponatraemia has been reported more frequently in women [19]. Consistent with these observations, females accounted for 71.4% of reported cases of mirtazapine-associated hyponatraemia in a systematic review albeit based on a limited number of cases [5]. The occurrence of probable mirtazapine-associated SIADH in the present elderly male patient is therefore noteworthy.

The baseline serum sodium level of 134 mEq/L before mirtazapine initiation may have represented a predisposing factor [20], however preexisting chronic hyponatraemia could not be established from this patient's available clinical information and the temporal association with mirtazapine initiation together with improvement following drug discontinuation supports mirtazapine as the likely precipitating factor.

Even though mirtazapine is commonly considered a safer alternative to other antidepressants induced hyponatraemia, baseline evaluation and regular follow-up monitoring of serum sodium levels along with vigilance of clinical signs of hyponatraemia should be performed, particularly in elderly patients and those with risk factors, especially during the first month after the initiation of mirtazapine. Continued clinical vigilance is also warranted as delayed presentations have been reported.

CONCLUSION(S)

This case highlights the potential of mirtazapine to cause symptomatic hyponatraemia through a probable SIADH mechanism even at a low dose of 3.75 mg/day. Although the onset of hyponatraemia may vary from days to months after treatment initiation, baseline serum sodium assessment with periodic follow-up monitoring together vigilance for clinical signs of hyponatraemia is warranted throughout treatment particularly during the first month in elderly patients and those with risk factors.

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