CASE REPORT

Citalopram-induced hyponatraemia and parkinsonism: potentially fatal side-effects not to be missed

Negin Damali Amiri,¹ Nishan Wijenaike²

¹Department of Neurosciences, Addenbrookes Hospital, Cambridge, UK

²Department of Diabetes & Endocrinology, West Suffolk Hospital, Bury St Edmunds, UK

Correspondence to
Dr Negin Damali Amiri,
neginda10@gmail.com

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SUMMARY

The use of selective serotonin reuptake inhibitors (SSRIs), such as citalopram, is on the rise and, as such, clinicians must be vigilant of rare side-effects associated with this group of medications. We report the case of a 65-year-old man who presented to West Suffolk Hospital with a fall, confusion and movement abnormalities, and was found to have a serum sodium of 105 on admission. He was managed with hypertonic saline, dopamine agonists and intensive physiotherapy. Despite initially deteriorating neurologically, he made a remarkable recovery, and was discharged home at his pre-admission baseline. The learning points from this report are as follows: (1) regular monitoring of electrolytes on starting an SSRI (and similarly selective noradrenaline reuptake inhibitors–SNRIs) in SSRI/SNRIs naïve patients, (2) awareness of possible citalopram-induced parkinsonism and the potential benefits of dopamine agonists as one management strategy and (3) vigilant fluid/electrolyte monitoring in patients with profound hyponatraemia.

of his gait was observed by his family. On further questioning there were reports of writhing movements of his right arm and lip smacking, but no fever, photophobia, headache, swallowing or speech difficulties, weakness or sensory loss. His medical history included hypertension and ankylosing spondylitis; he was on indapamide, lercanidipine and ramipril for his blood pressure, and a monthly injection of adalimumab for ankylosing spondylitis; he drank occasional alcohol and was a non-smoker.

On initial examination he appeared to have a vacant, hypomimic facial expression, somewhat oriented to person, but not to time or place. He had a mild resting tremor bilaterally and lip smacking; his pupils were equal and reactive, and all other cranial nerves as well as the remainder of the neurological examination were unremarkable. His neck was rigid with a limited range of movements; his respiratory, cardiovascular and abdominal examinations were normal; he was euvolaemic on admission.

BACKGROUND

Citalopram is increasingly commonly used as an antidepressant and as such, increasing number of patients will be affected by its potentially debilitating side-effects, however rare they may be. In general practice, patients are usually reviewed 4–6 weeks after starting citalopram to monitor the effect of this medication on mood. From our case study and similar published reports, however, early medication review to monitor for potentially adverse side-effects of hyponatraemia and movement disorders is therefore highly recommended. Caution must also be taken in patients with a primary movement disorder with depression who are considered for selective serotonin reuptake inhibitor (SSRI) therapy, as the risk of exacerbation of movement disorders is potentially high.

CASE PRESENTATION

A 65-year-old man presented to West Suffolk Hospital having had a fall 2 days prior to admission (no head injury or loss of consciousness were sustained); his wife gave a 4-week history of worsening nausea and weight loss, prompting our patient to visit his general practitioner. After investigations for this, including an oesophagogastroduodenoscopy, he was reassured and was started on citalopram to help his mood. A few days after starting citalopram, he became increasingly confused, reported blurred vision, and slowing and shuffling

INVESTIGATIONS

Initial biochemical investigations revealed serum sodium of 105 (135–145 mmol/L) and potassium of 3.6 (3.5–5.1 mmol/L). The patient's renal and liver function tests, and inflammatory markers were within normal range; serum osmolality was 220 (normal 275–295), with a urine osmolality of 377 (normal 300–900); he had urinary sodium of 39 (normal >20 mmol/L) and urinary potassium of 28 (normal 25–125 mmol/L); the results of a short synacthen test were within normal limits (cortisol basal: 941; cortisol 30 min postsynacthen injection: 1530) with normal thyroid-stimulating hormone and T4. The patient's pre-admission (Na), 4, 12 and 20 weeks prior to admission were 127, 128 and 135 mmol/L, respectively (please also see below for further investigation findings). A search of Drugs Interactions Checker did not reveal any interactions between citalopram and the patient's pre-admission medication.

DIFFERENTIAL DIAGNOSIS

Given an abnormally high urine osmolality in the presence of low serum sodium and osmolality, our working diagnosis at this stage was that of a syndrome of inappropriate antidiuretic hormone production (SIADH).

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TREATMENT

In the initial phase, our patient was catheterised and placed on fluid restriction with close monitoring of urine output, and 12 hourly monitoring of electrolytes; his antihypertensive medications and citalopram were stopped. His sodium improved to 110 and 108 in the subsequent 2 days, however, it dropped to 102 on day 3. At this point he was started on a very slow infusion of hypertonic saline (1.8% sodium chloride) and tolvaptan, which slowly increased his sodium levels to 109, 111 and 125 in the ensuing 72 h (figure 1). Despite the improvements in serum sodium concentrations, he deteriorated clinically from day 4 onwards: he became mute and unresponsive to external stimuli; his eyes were open, with intact blinking reflex, but without spontaneous eye movements; his pupillary reflexes were present and gag reflex intact; he was very rigid with brisk reflexes throughout. Furthermore, he was emotionally labile, with increasingly evident lip smacking; he had developed self-terminating myoclonic jerks in the upper limbs. At this point tolvaptan was stopped and a slow infusion of 0.9% saline continued.

Our patient remained unresponsive for over a week. He was fed through a nasogastric tube and reviewed by the neurologists. MRI could not be obtained due to the patient's severe neck rigidity, however, CT of the head, chest, abdomen and pelvis were reported as normal. He was started on an increasing dose of rotigotine patch to improve possible parkinsonian rigidity (maximum 4 mg/24 h). Within a day of starting the latter, he began to improve (he started taking oral fluids) and regained his ability to speak. He continued to improve neurologically in the ensuing 2 weeks, and made a remarkable recovery both clinically and biochemically. His serum sodium stabilised to around 134 mmol/L, and urine and serum osmolality returned to normal limits; his rotigotine patch was stopped as he began walking independently (and additionally due to experiencing reversible side-effects of obsessive compulsive disorder and disinhibition). He was discharged 4 weeks later with full gain of physical and cognitive function. His blood pressure was controlled on bisoprolol and amlodipine only; his monthly injection of adalimumab was restarted by the rheumatologists a few weeks after discharge and serum sodium remains stable to date (figure 1).

DISCUSSION

Low sodium levels in this case were attributed to the SIADH production for the following reasons: normal renal function, short synacthen test, low serum osmolality and a euvoalaemic fluid balance. The osmotic pressures caused by acute severe hyponatraemia and its rapid correction is a known entity, causing an osmotic demyelination syndrome (central pontine and extra-pontine myelinolysis—CPM and EPM, respectively).¹

The clinically acceptable rate of sodium correction is a much debated topic and is argued to be dependent on whether the rate of sodium decline is acute (<48 h) or chronic (>48 h), among other factors. This stems from the theory that in response to hyponatraemia, the process of establishing isotonicity across the neuronal cell membrane, and therefore adapting to the low sodium state to minimise cell swelling and death, takes approximately 48 h. If extracellular sodium is corrected faster than the rate at which electrolytes can be transported into neurons, cell shrinkage will occur; oligodendrocytes are particularly vulnerable to cell death and therefore highly myelinated sections of the brain (eg, pons) are mostly affected, resulting in the clinical manifestations seen.

Rapid correction in acute hyponatraemia is therefore acceptable, however, a slow rise of 8–10 mmol of sodium per day, in chronic hyponatraemia, has been agreed among physicians; this allows for sufficient time to re-establish a transmembrane gradient. (Readers are recommended to refer to an excellent review on the management of hyponatraemia and CPM/EPM, in the *JNNP* by RJ Martin,² and a review by Ellison *et al*.³ where authors have postulated various formulas for calculating the initial rate of sodium infusion).

Whether a patient experiences myelinolysis, and how well they recover from this phenomenon is, however, not solely dependent on the rate of correction, but on age, comorbidities, concomitant medications and the underlying cause of hyponatraemia.⁴ Our patient had signs indicative of CPM (confusion, mutism, quadriparesis, dysphagia) as well as EPM (tremor and cognitive dysfunction). From the history, the onset of severe hyponatraemia seems to have coincided with the start of citalopram, on a background of mild hyponatraemia of 127–128 mmol/L prior to the start of this medication, which could be attributed to the patient's antihypertensive medication.

Figure 1 [Na] in mmol/L during the patient's inpatient stay. The first arrow indicates the lowest sodium concentration of 102 mmol/L when hypertonic saline and tolvaptan were started; the second arrow indicates when hypertonic saline and tolvaptan were stopped. The third arrow delineates the serum sodium concentration at discharge, followed by outpatient monitoring of serum sodium.

His clinical symptoms of shuffling gait, tremor, writhing movements and bradykinesia, however, predated his admission and correction of sodium levels.

SSRIs and selective noradrenaline reuptake inhibitors (SNRIs) have been widely reported to cause SIADH,^{5–7} however, there are also 127 case reports of SSRI-induced movement disorders;⁸ one case report in particular reports citalopram-induced parkinsonism.⁹ The S-stereoisomer of citalopram, escitalopram, has also been reported in association with parkinsonism and hyponatraemia.^{10–11} In the latter case report the patient was on escitalopram for 2 weeks prior to symptom manifestation (tremor, rigidity and bradykinesia), and improved with intravenous injection of biperiden (a medication with anticholinergic properties used in the treatment of Parkinson's disease).

There is evidence from animal studies that serotonin transporter inhibitors, such as citalopram and fluoxetine, play a role in the downregulation of tyrosine hydroxylase (the rate limiting enzyme in dopamine synthesis). There is a report of increased microglial activity in the presence of SSRIs, and it is proposed that the increased activation may be responsible for the reduction in tyrosine hydroxylase activity in the substantia nigra and the striatum.¹² The latter in part explains the improvement in our patient's extrapyramidal manifestations on starting rotigotine (dopamine agonist). The citalopram-induced extra-pyramidal side-effects reported by Miletic *et al* were not associated with any electrolyte abnormalities. There are two reports of Dopa-responsive extrapyramidal side-effects of rapid sodium correction in SIADH caused by erythromycin. The extrapyramidal

side-effects seen in our patient may therefore be of two separate underlying aetiologies: (1) directly as a result of citalopram and (2) resulting from hyponatraemia or its correction. Dopamine precursors and agonists may therefore be used in the multifaceted management of parkinsonism caused by SSRIs and hyponatraemia (or its correction).

There appears to be no significant clinical difference among the SSRI family with regard to the incidence of SIADH; it is, however, recommended that should this side-effect occur, SNRIs are a suitable alternative (though this class of drugs are also reported to cause SIADH, albeit less frequently than SSRIs).⁷

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Contributors NW was the responsible consultant for the care of the patient and NDA the junior doctor on the team looking after the patient (at the time of working at West Suffolk Hospital as a foundation year 1 trainee). The manuscript was written by NDA and commented on by NW.

Competing interests None.

Patient consent Obtained.

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Learning points

- Regular monitoring of electrolytes on starting a selective serotonin reuptake inhibitor (SSRI) and selective noradrenaline reuptake inhibitor (SNRI) in SSRI/SNRI naïve patients.
- Awareness of possible citalopram-induced movement disorders, including parkinsonism and the potential use for dopamine-agonists in the acute management of SSRI-induced parkinsonism.
- Vigilant fluid/electrolyte monitoring in patients with profound hyponatraemia.
- Osmotic demyelinating syndrome can present with pontine as well as extrapontine clinical features.

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