

# Serotonin syndrome and acute hyponatremia, complex overlapping syndromes, a case report and review

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## ABSTRACT

**Objective:** To report the first case of simultaneous serotonin syndrome and acute hyponatremia secondary to sertraline and drug interactions resulting in patients' death (Naranjo ADR probability score 7). **Case Summary:** An 83-year-old female on sertraline for 5 years for depression was admitted for left tibial plateau fracture. She had a history of short bowel syndrome, total parenteral nutrition and CKD stage 3 secondary to vascular disease. 2 weeks post operatively, she developed into difficulty concentrating, tachycardia, hyperreflexia and clonus in context of opioids and antiemetic use but was afebrile and haemodynamically stable. She also developed into acute hyponatremia from 133 mmol/L to 127 mmol/L within 24 hours. Sertraline and antiemetic medications were stopped and cyproheptadine and diazepam were started to treat serotonin syndrome. The patient deteriorated after an initial improvement. She developed into aspiration pneumonia later and passed away in ICU. **Discussion:** Both acute hyponatremia and serotonin syndrome share SSRIs as common etiology, which have acute onset and rapid resolution and show multiple overlapping neurological features. Hunter criteria are more accurate than Sternbach criteria due to less emphasis on mental features to diagnose serotonin syndrome with overlapping conditions with similar presentation. Hyponatremia causes muscle weakness with hyporeflexia compared to serotonin syndrome with hyperreflexia and clonus. **Conclusion:** Clinicians should be aware of possibility of both acute hyponatremia and sero-

tonin syndrome secondary to SSRIs interacting with opioids and ondansetron. The use of Hunter criteria would aid in prompting diagnosis and initiation of timely treatment.

## KEYWORDS

Sertraline; Hyponatremia; Serotonin Syndrome

## 1. BACKGROUND

Serotonin syndrome is the result of overstimulation of 5-HT<sub>1A</sub> receptors by selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOI) or other serotonergic agents. The use of SSRIs is related to the frequency of the syndrome. Regardless of age or sex, onset is observed within 24 hours following the administration or overdose of a serotonergic agent [1]. Serotonin syndrome is characterized by a triad of mental, autonomic and neurological disorders. In order to reach a diagnosis of serotonin syndrome, a history of use of a serotonergic agent, recognized signs and symptoms, and the exclusion of other conditions are required [2]. Use of SSRIs in elderly has been associated with hyponatremia secondary to syndrome of inappropriate antidiuretic syndrome (SIADH). SIADH is defined as less than maximally diluted urine in the presence of plasma hypotonicity (<280 mOsm/kg) and hyponatremia (<135 mEq/L). Diagnosis is contingent on the absence of volume depletion or overload, emotional stress or pain, or diuretics or other drugs that stimulate antidiuretic hormone secretion [3]. There have been no case reports documenting the presence of simultaneous serotonin syndrome and acute hyponatremia in elderly patients secondary to SSRIs. We describe the first reported clinical case of patient on SSRI developing into

both acute hyponatremia and serotonin syndrome.

## 2. METHODS

Pubmed and MEDLINE were searched for the following words

- 1) "Serotonin toxicity and SSRI"
- 2) "Serotonin syndrome and sertraline"
- 3) "Hyponatremia due to SSRI"
- 4) "Hyponatremia due to sertraline"
- 5) "Serotonin syndrome and hyponatremia due to SSRI"
- 6) "Serotonin syndrome and hyponatremia due to sertraline"

Australian Register of Therapeutic Goods were contacted and following questions were asked

- 1) When were SSRIs added to the Australian Register of Therapeutic Goods?
- 2) When was sertraline added to Australian Register of Therapeutic Goods?
- 3) What is the number of reports of serotonin syndrome associated with sertraline in the last 10 years in the Database of Adverse Event Notifications (DAEN)?
- 4) How many cases of hyponatremia associated with sertraline have been reported in the Database of Adverse Event Notifications (DAEN) in the last 10 years?
- 5) In how many cases was Sertraline the sole suspected medication for hyponatremia?
- 6) What is the number of cases where death was the reported outcome for hyponatremia and sertraline notification?
- 7) What is the number of cases where death was the reported outcome for serotonin syndrome and sertraline notification?
- 8) What is the number of cases in the TGA database coded as both hyponatremia and serotonin syndrome where SSRIs were a suspected medication?
- 9) What is the number of cases in the TGA database coded as both hyponatremia and serotonin syndrome where sertraline was a suspected medication?

## 3. RESULTS

*Pubmed and MEDLINE search results on 19/12/2013 at 13:00 pm*

- 1) "Serotonin toxicity and SSRI" showed 837 articles
- 2) "Serotonin syndrome and sertraline" showed 91 articles
- 3) "Hyponatremia due to SSRI" showed 228 articles
- 4) "Hyponatremia due to sertraline" showed 31 articles
- 5) "Serotonin syndrome and hyponatremia due to SSRI" one case report mentioning serotonin syndrome and hyponatremia in a psychiatric patient but in context of drug overdose with full recovery alter on.

- 6) "Serotonin syndrome and hyponatremia due to sertraline" showed no articles.

*Australian Register of Therapeutic Goods search results*

- 1) SSRIs were added to the Australian Register of Therapeutic Goods in 5 September 1991.
- 2) Sertraline was added to Australian Register of Therapeutic Goods on 24 November 1993.
- 3) The number of reports of serotonin syndrome associated with sertraline in the last 10 years in the Database of Adverse Event Notifications (DAEN) was 54.
- 4) Cases of hyponatremia associated with sertraline have been reported in the Database of Adverse Event Notifications (DAEN) in the last 10 years were 61.
- 5) The number of cases where death was the reported outcome for serotonin syndrome and sertraline notification was zero.
- 6) The number of cases where death was the reported outcome for hyponatremia and sertraline notification was 2.
- 7) The number of cases in the TGA database coded as both hyponatremia and serotonin syndrome where SSRI or sertraline was a suspected medication were zero.

## 4. CASE REPORT

An 83-year-old (weight 68 kg) female was admitted to orthopaedics unit for left tibial plateau fracture secondary to a mechanical fall. Past medical history comprised of short bowel syndrome due to mesenteric artery thrombosis leading to intestinal resection. She also had total parenteral nutrition related biliary cirrhosis, CKD stage 3 secondary to vascular disease. Other conditions included atrial fibrillation on aspirin, hypothyroidism, essential tremors, depression and chronic diarrhoea. She had been on a stable dose of sertraline 100 mg once daily for 2 years with no prior antidepressant treatment. The regular medication list consisted of metoprolol 12.5 mbd, aspirin 100 mg od, thyroxine 100 mcg od, ursodeoxycholic acid 250 mg tds.

She underwent open reduction and internal fixation of the left tibia. She was started on endone 5 mg tds PRN for analgesia and ondansetron 8 mg tds with promethazine 10 - 25 mg PRN 8 hrly due to ongoing chronic nausea worsened post operatively.

2 weeks post operatively, patient' tremor and chronic diarrhoea became worse. She also developed, difficulty concentrating, but was oriented in person and place. She had tachycardia but haemodynamically stable and afebrile. She had fluctuating orientation to time, place, and person and hyperreflexia but no other abnormal focal neurology. Blood tests showed development of acute hyponatremia from 133 mmol/L to 127 mmol/L within 24 hours.

Patient was managed with fluid restriction. She had a

further drop in serum sodium to 122 mmol/litre in the next 24 hours. Patient was diagnosed as SIADH in presence of normal cortisol, TFTs, CT brain, euvloemia and hyperosmolar urine.

Patient developed inducible clonus, myoclonus, and dilated pupils but no fever in the next 24 hours. Patient was diagnosed as serotonin syndrome based on clinical features and use of sertraline with ondansetron on background of opioids use.

She was managed by stopping sertraline and antiemetic medications, fluid restriction and was also started on cyproheptadine and diazepam.

Patient's sodium levels became normal (135 mmol/L) in response to these measures within the next 48 hours. Her agitation, confusion and tremors improved. Her tachycardia resolved but the clonus persisted.

Patient developed aspiration pneumonia on the fifth day after onset of symptoms. Patient deteriorated further ending up in ICU. Patient and family elected for comfort measures and patient passed away.

## 5. DISCUSSION

To our knowledge this is the first reported case of serotonin syndrome and hyponatremia secondary to sertraline presenting concurrently and presenting a dilemma in terms of diagnosis. According to Naranjo probability scale, the combination of sertraline and ondansetron with promethazine was highly probable (score 7) as the cause of both serotonin syndrome and acute hyponatremia [4].

Serotonin syndrome and acute hyponatremia can both overlap in the clinical presentation which was the diagnostic dilemma in our patient. There is no specific test for serotonin syndrome. An elevation of the total creatine kinase and leukocyte count and elevated transaminase levels or lower bicarbonate levels has been reported [5].

Both serotonin syndrome and acute hyponatremia can develop over 24 hours [5]. In most cases hyponatremia resolves quickly upon correction of underlying etiology [6]. Most patients with serotonin syndrome patients improve completely within 24 hours after being admitted [7]. Both conditions can present as lethargy, confusion, impaired concentration, dizziness, fatigue, forgetfulness, nausea, muscle cramps and headache. Both can cause ataxia, nystagmus, tremor, rigidity and aphasia and up going planters bilaterally [8,9].

This was the case in our patient who became unwell acutely. She had features of lethargy, confusion, impaired concentration, dizziness, fatigue, forgetfulness, nausea, muscle cramps and headache. She also had cause ataxia, tremor, and up going planters bilaterally.

Inclusion of four points in sternbach criteria relate to mental status, which bends the definition towards patients with an abnormal mental state. This makes it difficult to diagnose serotonin syndrome with overlapping

conditions with similar presentation.

Hyponatremia typically causes generalized cerebral oedema. Focal neurologic signs have also been reported in hyponatremia without a structural lesion and include hemiparesis, monoparesis, ataxia, nystagmus, tremor, rigidity, aphasia, and unilateral corticospinal tract signs [9,10]. Muscle symptoms other than cramps are uncommon [11]. Rigidity, tremors, myoclonus, asterixis and chorea have been associated with hypernatremia [12]. In general, the fall rate of serum sodium, rather than the absolute magnitude of the fall, appears to be the most important predictor of symptoms [5]. Hyponatremia causes muscle weakness with hyporeflexia. Muscular symptoms are mostly restricted to cramps, compared to serotonin syndrome with hyperreflexia and clonus [13]. This was the case in our patient who had hyperreflexia and clonus.

Hunter Criteria are most accurate (84 percent sensitive and 97 percent specific when compared with the gold standard of diagnosis by a medical toxicologist) compared to sternbach criteria and have less emphasis on mental features [7]. In our patient, the history of use of SSRI and inducible clonus were strongly suggestive of serotonin syndrome.

The principal differential diagnosis in context of promethazine use was neuroleptic malignant syndrome (NMS). Common criteria are alteration of consciousness, diaphoresis, autonomic instability, hyperthermia and elevated creatine kinase levels. NMS is observed most often following a rapid increase in dosage of a neuroleptic drug. These symptoms appear within 7 days in 66% of cases. Our patient was taking promethazine associated with NMS, but the absence of hyperthermia and muscular rigidity and the presence of diarrhoea and myoclonus were indicators of serotonin syndrome [7].

Our patient was taking a stable dose of sertraline for 5 years but serotonin syndrome has been reported in therapeutic and sub therapeutic doses. She developed serotonin syndrome secondary to ondansetron which has been associated with this syndrome [8]. She was also placed on endone 5 mg tds post operatively which has been reported as causative in certain reported cases. To our knowledge this is the sixth case report of endone induced serotonin syndrome. The short-term effect of morphine and perhaps other opioids is to increase serotonin release in widespread areas of the forebrain [14].

The mortality of severe serotonin syndrome is estimated to range from 2% to 12%. Treatment is guided by the severity of presentation. Supportive care, including intravenous fluids, is indicated in patients with vital sign abnormalities. Neurological symptoms, including serious myoclonus and hyperreflexia, are sometimes treated with benzodiazepine. Hyperthermia should be aggressively managed with external cooling, hydration, and benzodiazepines. Patients with a temperature higher than 41°C

should be intubated with induced neuromuscular paralysis. There is a limited role for traditional antipyretics, as the mechanism of serotonin syndrome is due to muscle tone rather than central thermoregulation. The cyproheptadine, should be considered in moderate cases and is recommended in severe cases, despite a lack of randomized controlled trial evidence [15].

Antidiuretic hormone levels are universally elevated post-operatively when compared with pre-operative values [9]. Adults older than age 65 appear most vulnerable to developing hyponatremia in association with the use of SSRIs and the risk appears to increase with age [3]. In general, adverse drug reactions are reported to occur more frequently in female patients. Hyponatremia associated with SSRI use usually develops soon after the start of drug therapy. Three quarters of the cases presented within 30 days after the start of therapy. However, hyponatremia may occur late in the course of SSRI therapy which is the case in our patient [16]. For each SSRI the proportion of spontaneous reports of adverse reactions received by the WHO documenting hyponatremia or SIADH was similar [16].

Other risk factors for hospital-acquired hyponatremia in our patient were an increase in CRP and the use of antibiotics and opioids. These factors represent interesting new clues regarding the pathophysiology of hospital acquired hyponatremia, suggesting that the acute-phase response, pain and/or direct drug effects could be involved in the release of antidiuretic hormone [17].

For hyponatremia the treatment should be directed based on the neurological involvement and not the absolute serum sodium; and hypertonic saline is not indicated in the asymptomatic patient who is neurologically intact, regardless of the serum sodium. Symptomatic hyponatremia, on the other hand, is a medical emergency. Once signs of encephalopathy are identified, prompt treatment is required in a monitored setting before imaging studies are performed. Fluid restriction alone has no place in the treatment of symptomatic hyponatraemia. If symptomatic hyponatraemia is recognized and treated promptly, prior to developing a hypoxic event, the neurological outcome is good. Patients with symptomatic hyponatraemia should be treated with hypertonic saline (3%, 514 mEq/l) using an infusion pump. The rate of infusion should continue until the patient is alert and seizure free. In patients who are actively seizing or with impending respiratory arrest, the serum sodium can be raised by as much as 8 - 10 mEq/l in the first 4 h, but the absolute change in serum sodium should not exceed 15 - 20 mEq/l in the first 48 hrs [9].

## 6. CONCLUSION

Both serotonin syndrome and acute hyponatremia are SSRI mediated. Both conditions have an acute onset,

showing multiple overlapping clinical features and are potentially life-threatening. A high index of suspicion and less emphasis on mental features will aid in differential diagnosis. Clonus and hyperreflexia are more suggestive of serotonin syndrome compared to acute hyponatremia. Both conditions have good prognosis if treatment is initiated in a timely fashion, and this case report highlights the potential pitfalls in the management of the two complex overlapping syndromes.

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## CONFLICT OF INTEREST

None.

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