

## •Case report•

## Hyponatremia with olanzapine - A suspected association

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**Summary:** Hyponatremia is a rare, yet potentially life threatening complication of antipsychotics. Here, we report a case of a 45-year-old female diagnosed with schizophrenia who developed hyponatremia soon after addition of olanzapine to the existing treatment. This prompted us to evaluate the relationship between hyponatremia and olanzapine, as timely management is crucial. Naranjo algorithm established a “probable” causal relation between olanzapine and hyponatremia. Possible etiological reasons of this clinically significant and life threatening adverse event have been discussed. We report the case and the literature focusing on hyponatremia as a possible adverse event of olanzapine. Medical illnesses are often ignored or missed in patients with psychiatric disorders either due to patients’ inability to report complaints or non-serious attitude of physicians towards such patients. A high index of suspicion should be kept while dealing with this probable complication.

**Key words:** Hyponatremia, Olanzapine, Antipsychotics, India

[*Shanghai Arch Psychiatry*. 2017; **29**(3): 177-179. doi: <http://dx.doi.org/10.11919/j.issn.1002-0829.216053>]

### 1. Case history

A 45-year-old married Hindu female, non-smoker, non hypertensive and non diabetic, was diagnosed with paranoid schizophrenia, for which she was maintaining well on tablet haloperidol 20 mg/day for the last 5 years. The total duration of illness was around 7 years, with a drug naive period of approximately 2 years. Around three months ago, the patient’s symptoms had become exaggerated as she had not taken her antipsychotic medication for approximately 8-10 days because she was out of town and did not have her medicines with her. Her complaints were sleep disturbance, referential and persecutory ideas with intermittent auditory hallucinations and episodes of irritability with aggressive behavior. The patient presented to the hospital after which haloperidol was started again at 10 mg/day, increased to 20 mg/day and maintained for the next month. However no significant improvement was reported this time using haloperidol. Olanzapine 5

mg/day was added and increased to 10 mg/day within 2 weeks. One month after adding Olanzapine, the patient developed symptoms of nausea, anorexia and weakness. However there were no episodes of vomiting or diarrhea. Also, there was no significant decrement in diet. The symptoms exacerbated over the next 2 weeks along with muscle cramps, unsteady gait and fluctuating orientation.

The patient was admitted to emergency services for evaluation. Her physical examination revealed tachycardia (pulse - 118/min), low blood pressure (94/60 mm hg), dehydration, and disorientation to time. Her systemic examination was unremarkable. Her blood tests revealed low serum sodium of 120 mmol/l (135-150 mmol/l). The results of the remaining tests were within normal limits (including renal function tests, liver function tests, serum concentrations of potassium, blood sugar, total proteins and lipids). Treatment was started on the diagnosis of probable normovolemic

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hyponatremia as physical examination did not reveal any signs of fluid overload. The electrocardiography revealed only sinus tachycardia and plasma osmolality was reported to be 288 mOsm/kg H<sub>2</sub>O (285–295 mOsm/kgH<sub>2</sub>O). She was started on 3% NaCl infusion over the initial few hours until achieving full consciousness followed by normal saline. Fluid restriction and oral salt supplement was advised. The patient recovered in 2 days with serum sodium levels of 140 mmol/l. However, the exact reason for hyponatremia could not be established even after detailed investigations (including thyroid function tests). Olanzapine continued to be administered, except for the day emergency treatment was given. Upon detailed assessment, the patient's diet was found to be consistently good over these years, and even during the last 2 weeks. No specific diet/salt restriction was reported.

A week later, the patient again had similar episode of hyponatremia (serum sodium of 116 mmol/l) while continuing on the antipsychotics. She had to be managed in the emergency room with similar procedures and protocols. With no evident organic cause for the hyponatremia, a literature search was carried out and Olanzapine was postulated as a potential agent. It was planned to stop Olanzapine and observe the patient, while continuing medical management for hyponatremia. Within 3 days of stopping Olanzapine, the patient improved and never had a recurrence of hyponatremia over the next 6 months follow up. She was maintained on haloperidol 20 mg/day and risperidone 4 mg/day thereafter. Naranjo algorithm<sup>[1]</sup> established a “probable” causal relation between the drug and adverse event, with a total score of 8 (suggestive of a probable relationship).

## 2. Discussion

Olanzapine is a commonly used atypical antipsychotic for patients with schizophrenia and other psychotic disorders. In the CATIE study (Clinical Antipsychotic Trials of Intervention Effectiveness), Olanzapine was found to have the lowest discontinuation rate, possibly due to fewer incidences of acute side effects.<sup>[2]</sup> Still, life threatening adverse effects such as hyponatremia may limit its safe and effective use. A systematic review of evidence for antipsychotic induced hyponatremia from 1974 to 2003, found more cases of hyponatremia with typical compared to atypical antipsychotics.<sup>[3]</sup>

Hyponatremia is the commonest electrolyte imbalance encountered in medical emergencies.<sup>[4]</sup> It is characterized by a plasma sodium concentration less than 135 mEq/L<sup>[5]</sup> and manifests clinically with neurological and systemic symptoms such as nausea, vomiting, anorexia, headache, disorientation, confusion, irritability and lethargy.<sup>[6]</sup> Profound hyponatremia may manifest as severe mental status changes including confusion, delirium, seizure, coma, and death. The most common causes of hyponatremia are fluid loss and dehydration, congestive heart failure, liver and renal

failure, and Syndrome of inappropriate anti-diuretic hormone.

Hyponatremia as a potential adverse event from the use of antipsychotics has not been greatly researched. Only a few case reports/series are available.<sup>[7,8]</sup> Meulendijks and colleagues did a systematic review of evidence for antipsychotic induced hyponatremia from 1974 to 2003 and found that both typical (58 case reports) and atypical antipsychotics (10 case reports) were implicated in hyponatremia and the association was independent of age or gender or dose.<sup>[3]</sup> Many antipsychotics (both typical and atypical) like chlorpromazine, fluphenazine, haloperidol, trifluoperazine, amisulpride, olanzapine and risperidone have been implicated.<sup>[3,9]</sup> Hyponatremia is postulated to be caused by blockade of inhibitory effect of dopamine on release of anti-diuretic hormone (ADH) by antipsychotics.<sup>[10]</sup> Clozapine, because of its low affinity for D2 receptors, is less prone to causing hyponatremia and may improve associated polydipsia. However on the contrary, it has been demonstrated in rats that dopamine could have a stimulatory effect on ADH release.<sup>[11]</sup> Therefore, the exact mechanism of antipsychotic-induced hyponatremia is still unclear.

In the index case, hyponatremia and olanzapine were temporally associated, still it is difficult to establish the exact offending medication. Haloperidol is also a known culprit that is described in some case reports. However, haloperidol alone did not produce hyponatremia nor did it in combination with risperidone suggesting that olanzapine may have a stronger causal relation with hyponatremia. Also, Naranjo algorithm established a “probable” causal relationship with olanzapine. Another possible mechanism is that olanzapine precipitated hyponatremia in a predisposed individual taking haloperidol, and the causality may be attributed to the combined effect of both olanzapine and haloperidol.

Hyponatremia is a rare yet clinically important adverse reaction to treatment with psychotropic drugs. It is a potentially dangerous medical complication in psychiatric patients. Psychogenic polydipsia is an important differential diagnosis, as it is characterized by similar symptoms of polydipsia and polyuria. Also, psychogenic polydipsia is commonly found in psychiatric patients, more likely in schizophrenia.<sup>[12]</sup> Multiple other factors such as diet, salt intake, ageing comorbid conditions (smoking, diabetes) or concurrent medications may also play a role and should be considered.<sup>[13]</sup> There is a complete and rapid recovery of drug induced hyponatremia once the offending agent is discontinued, as happened with the index case, without any further recurrences. Clinicians need to be aware of this dangerous complication and exercise caution when prescribing psychotropic drugs.

## Funding statement

No funding support was obtained for preparing this case report.

**Conflict of interest statement**

The authors declare that they have no conflict of interest related to this manuscript

**Informed consent**

The patient and his guardian signed an informed consent form and agreed to the publication of this case report.

**低钠血症与奥氮平——可能的关联**

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**概述：**低钠血症是一种罕见的具有潜在生命危险的抗精神病药物治疗的不良反应。这里，我们报告一个病例，45岁女性精神分裂症患者在接受奥氮平治疗后不久出现低钠血症。为此我们评估了低钠血症和奥氮平治疗之间的关系，因为及时的药物监测至关重要。根据Naranjo算法，在奥氮平和低钠血症之间的关联性评价，可评价为“可能”。因此有必要探究低钠血症这一临床上重

大、危及生命的不良事件产生的可能原因。我们报告的病例聚焦于奥氮平治疗引起的低钠血症的不良事件。由于精神疾病患者有时无法主诉或主诉不被重视，内科疾病常常被忽视或错过。在处理这种可能的不良反应时，应保持高度警觉性。

**关键词：**低钠血症；奥氮平；抗精神病药

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