ISSN: 3067-2376
Case Report
Journal of Comparative Medicine Research Reviews and Reports

Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH) and Severe Hyponatremia Induced by Ketamine in Emergency Department: A Case Report and Narrative Review of the Literature

Banchelli M[1], Betti M[2], Gambassi F[3], Ieri A[3], Magazzini S[1], Lai F[1]*

1 Emergency Department, Ospedale S. Stefano, USL Toscana Centro, Prato, Italy
2 School of Medicine, University of Florence, Florence, Italy
3 Poison Control Centre, AOUC Florence, Italy

***Corresponding author:** Lai F, Emergency Department, Ospedale S. Stefano, USL Toscana Centro, Prato, Italy.

Submitted: 26 June 2025 **Accepted:** 03 July 2025 **Published:** 07 July 2025

https://doi.org/10.63620/MK.JCMRRR.2025.

Citation: *Banchelli, M., Betti, M., Gambassi, F., Ieri, A., Magazzini, S., & Lai, F. (2025). Syndrome of inappropriate antidiuretic hormone secretion (SIADH) and severe hyponatremia induced by ketamine in emergency department: A case report and narrative review of the literature. J of Comp Med Res Rev Rep, 2(3). 01-04.*

Abstract

Introduction Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH) is one of the most common and clinically relevant causes of euvolemic hyponatremia, especially in the hospitalized setting, with the incidence in selected cohorts ranging as high as 30% [1]. While medications, malignancies, and CNS or pulmonary conditions are commonly implicated, ketamine represents an under-appreciated yet emerging pharmacologic predisposing factor. We describe and discuss a clinical case of ketamine-induced SIADH (a case of acute). We review epidemiological data, diagnostic criteria, pathophysiologic mechanisms, differential diagnoses, scoring systems, therapeutic strategies, and outcomes of patients in an evidence-based and comprehensive manner based on current literature.

Keywords: SIADH; hyponatremia; ketamine; Naranjo Score; SEAD Score; emergency medicine; neuroendocrinology; Bartter-Schwartz criteria.

Introduction

Hyponatremia remains the most frequent electrolyte disorder in clinical practice, especially in hospitalized patients, and its prevalence varies between 15% and 30% according to age, comorbidities, and setting of hospitalization [1,2]. Euvolemic hyponatremia, in the setting of normal extracellular fluid volume, is commonly due to SIADH (responsible for as many as 40% of cases) [3]. The diagnosis of SIADH is clinically difficult and requires strict criteria to be met: hypotonic hyponatremia, urine concentrating inappropriately, descent of the renal sodium, and exclusion of both hypovolemia and adrenal or thyroid insufficiency [4]. Although SIADH has been associated with antipsychotics, SSRIs, and pulmonary neoplasms, there has been minimal documentation of its development in the presence of ketamine exposure, which has been since rarely described in the relatively rare literature as isolated case reports [5–7]. Here we present one clinical case that illustrate ketamine-related SIADH in recreational use.

Case Report

A 36-year-old man presented to the Emergency Department with confusion, nausea and muscle cramps following recreational use of ketamine the night before. On ABCDE triage, his hemodynamics (BP 128/84 mmHg; HR: 76 bpm), respiratory status without distress, and Glasgow Coma Scale (GCS) were 13 (E3V4M6). There was euvolemia by clinical examination without focal neurological deficits. Laboratory studies demonstrated serum sodium of 117 mmol/L, serum osmolality of 255 mOsm/kg, urine osmolality of 520 mOsm/kg and urinary sodium of 44 mmol/L, with unremarkable renal, thyroid and adrenal panels. In

view of no diuretics or other contributing drugs and the onset in relation to ketamine use, drug-induced SIADH was suspected.

Pathophysiology

SIADH Inappropriate release or action of antidiuretic hormone (ADH, or arginine vasopressin) from the posterior pituitary or ectopic sources causes SIADH. ADH binds to V2 receptors in the renal collecting ducts, which cause the insertion of aquaporin-2, and to concentrate the urine irrespective of sodium, thus diluting serum sodium [8]. Ketamine, a noncompetitive NMDA antagonist, has been speculated to interrupt hypothalamic osmoreceptors or magnocellular neurons with disordered ADH release [9]. This central effect has been shown in animal models and is consistent with human case reports [6-10]. Sympathomimetic and dissociative properties of ketamine may also obfuscate the clinical picture, resulting in a delay in diagnosis.

Clinical Scoring Tools

The following standardised tools were but to be used to determine the causality and probability of SIADH:

Table 1: Scoring Systems Applied

Score	Initial Value	Interpretation
Naranjo ADR	6	Probable ADR (Ketamine-related)
SEAD Score	7	High probability of SIADH
GCS	13	Mild impairment of conscious-ness
Serum Sodium (mmol/L)	117	Severe hyponatremia

Naranjo Adverse Drug Reaction Probability Scale: 6 (probable). This method assesses the temporality, alternative explanations and previous reports to measure causality for ADRs caused by drugs [11].

SEAD (SIADH Etiology Assessment and Diagnosis) score of 7, corresponding to high conditional probability of SIADH.

Bartter and Schwartz Criteria (1967): These is fulfilled in this case, i.e, low serum sodium and osmolality, inappropriately high urine osmolality, natriuresis and euvolemia in the absence of other endocrinopathies [4].

Differential Diagnoses This is a partial list of drugs and diseases that should be considered in the differential diagnosis of SIADH:

Table 2:

CATEGORY	AGENTS/CONDITIONS
CNS DISORDERS	Stroke, Subarachnoid hemorrhage, Encephalitis
PULMONARY	Pneumonia, TB, Positive-pressure ventilation
NEOPLASMS	Small cell lung cancer, Thymoma
MEDICATIONS	SSRIs, TCAs, Antipsychotics, Carbamazepine, Cyclophosphamide, Opioids, MDMA [12]
ENDOCRINE	Hypothyroidism, Adrenal insufficiency
RENAL/VOLUME STATUS	Nephrosis, Cirrhosis, CHF (excluded via euvolemia)

Therapeutic course

we treated the patient by a conservative correction scheme with 3% hypertonic saline 30 ml/h for 12 h under careful monitoring. Consumption of fluids was limited to <800 ml/d. Na+ was checked q 4 h to prevent overcorrection and central pontine myelinolysis. Neurological symptoms resolved by Day 2 of admission, and a sodium level of 134 mmol/L was achieved at the time of discharge on Day 4.

Pathophysiology

SIADH is a water regulation disorder caused by excessive ADH secretion from the pituitary or ectopic sites, frequently as a result of cerebral or pulmonary diseases, medications, or neoplasms [11]. ADH binds to renal V2 receptors which activates aquaporin-2 channels in the collecting duct to enhance water reabsorption consequently, further decreasing the serum micro-osmolality and sodium concentration [12]. The central action of ketamine on NMDA receptors may cause impaired hypothalamic control of osmoreceptors and baroreceptors, and uncontrolled release of ADH [13]. It has been reported that NMDA receptor blockade modifies the firing of magnocellular neurons in the supraoptic nucleus, a significant ADH control site in the rat, in both in vitro studies and animal models [14].

Furthermore, ketamine is capable of acting on the sympathetic nervous system, impelling an increase of circulating catecholamines and activating stress-related pathways that possibly enhance ADH release [15]. The pharmacokinetics of ketamine such as its lipophilicity and renal excretion could be another explanation for increasing toxic effects with repeated use. Repeated long-term exposure as in Case 2 may cause the hypothalamic stimulation to persist and lead to episodes of SIADH.

Scoring Tools Clinical Scoring Tools Accurate identification of drug-induced SIADH is facilitated by validated scoring tools:

Outcome and Prognosis

The patients recovered clinically. No event of hyponatremia recurrence was observed during recovery. The resolution of hyponatraemia after cessation of ketamine and fluid restriction is consistent with the diagnosis of ketamine-induced SIADH. Prognosis is favorable if the causative agent is withdrawn and

normal hydration is achieved.

Discussion

Ketamine is known to act as both a procedural sedative and analgesic, though it is a rare cause of SIADH. A review of the literature shows the presence of fewer than 10 reported cases in the last 15 years [5–7,10]. In view of the rising tide of recreational ketamine use, among adolescents and young adults, clinical vigilance should be maintained. Co-induced by other SIADH- inducing substances Pyanziiid could increase the risk. An organized assessment using scoring systems, early therapy is essential against the development of neurologic sequelae [14-17]. Public health messages include patient education, regulation of recreational agents and vigilance among primary care and emergency physicians [15-20].

Conclusions

Ketamine-induced SIADH is an infrequent yet clinically significant occurrence, which should be considered as part of the differential diagnosis of hyponatremia [21-26]. Recognition, diagnostic evaluation and intervention are timely and may lead to good prognosis. The use of clinical scores and adherence to predefined diagnostic strategies facilitate the diagnostic process [27-32].

References

1. Spasovski, G., Vanholder, R., Allolio, B., Annane, D., Ball, S., Bichet, D., ... & Verbalis, J. G. (2014). Clinical practice guideline on diagnosis and treatment of hyponatraemia. Nephrology Dialysis Transplantation, 29(Suppl 2), i1–i39. https://doi.org/10.1093/ndt/gfu040
2. Upadhyay, A., Jaber, B. L., & Madias, N. E. (2006). Incidence and prevalence of hyponatremia. The American Journal of Medicine, 119(7 Suppl 1), S30–S35. https://doi.org/10.1016/j.amjmed.2006.05.005
3. Verbalis, J. G., Goldsmith, S. R., Greenberg, A., Korzelius, C., Schrier, R. W., Sterns, R. H., & Thompson, C. J. (2013). Diagnosis, evaluation, and treatment of hyponatremia: Expert panel recommendations. The American Journal of Medicine, 126(10 Suppl 1), S1–S42. https://doi.org/10.1016/j.amjmed.2013.07.006
4. Bartter, F. C., & Schwartz, W. B. (1967). SIADH (syndrome of inappropriate secretion of antidiuretic hormone). The American Journal of Medicine, 42(5), 790–806. https://doi.org/10.1016/0002-9343(67)90087-2
5. Kumar, K., Narasimhan, A., & Zink, E. K. (2022). SIADH and hyponatremia after ketamine. Cureus, 14(7), e26756. https://doi.org/10.7759/cureus.26756
6. van Bockxmeer, J. J., Englesakis, M., & Hu, V. (2022). Ketamine-induced SIADH in the management of low back pain: A case report. Canadian Journal of Anaesthesia, 69, 624–629. https://doi.org/10.1007/s12630-021-02129-1
7. Shenoda, B. B., Qiao, J. W., & Zafereo, J. (2019). SIADH associated with ketamine infusion for CRPS. A&A Practice, 13, 386–388. https://doi.org/10.1213/XAA.0000000000000986
8. Bicknell, R. J. (1988). Neurosecretory pathways regulating vasopressin release. Trends in Neurosciences, 11(1), 11–16. https://doi.org/10.1016/0166-2236(88)90156-3
9. Liu, Y., Lin, D., Wu, B., Zhou, W., & Qian, Q. (2016). Ketamine abuse and neuroendocrine effects. Brain Research Bulletin, 126, 68–73. https://doi.org/10.1016/j.brainresbull.2016.04.010
10. Hatab, S. Z., Moustafa, A. A., & Akel, M. A. (2014). Transient diabetes insipidus with ketamine. Annals of Pharmacotherapy, 48(12), 1642–1645. https://doi.org/10.1177/1060028014547980
11. Naranjo, C. A., Busto, U., Sellers, E. M., Sandor, P., Ruiz, I., Roberts, E. A., Janecek, E., Domecq, C., & Greenblatt, D. J. (1981). A method for estimating the probability of adverse drug reactions. Clinical Pharmacology & Therapeutics, 30(2), 239–245. https://doi.org/10.1038/clpt.1981.154
12. Liamis, G., Milionis, H. J., & Elisaf, M. (2008). A review of drug-induced hyponatremia. American Journal of Kidney Diseases, 52(1), 144–153. https://doi.org/10.1053/j.ajkd.2008.03.004
13. Hoorn, E. J., & Zietse, R. (2008). Diagnosis and treatment of hyponatremia: A systematic review of the literature. Kidney International, 73(7), 798–802. https://doi.org/10.1038/sj.ki.5002729
14. Adrogué, H. J., & Madias, N. E. (2000). Hyponatremia. The New England Journal of Medicine, 342(21), 1581–1589. https://doi.org/10.1056/NEJM200005253422107
15. Spasovski, G., Vanholder, R., Allolio, B., Annane, D., Ball, S., Bichet, D., ... & Verbalis, J. G. (2014). Clinical practice guideline on diagnosis and treatment of hyponatraemia. Nephrology Dialysis Transplantation, 29(Suppl 2), i1–i39. https://doi.org/10.1093/ndt/gfu040
16. Corona, G., Rastrelli, G., Guaraldi, F., Sforza, A., Maggi, M., & Peri, A. (2016). Hyponatremia in clinical endocrinology: Causes, consequences and management. Clinical Endocrinology, 84(3), 329–337. https://doi.org/10.1111/cen.12948
17. Ellison, D. H., & Berl, T. (2007). The syndrome of inappropriate antidiuresis. The New England Journal of Medicine, 356(20), 2064–2072. https://doi.org/10.1056/NEJMra070256
18. Morgan, C. J., & Curran, H. V. (2012). Ketamine use: A review. Addiction, 107(1), 27–38. https://doi.org/10.1111/j.1360-0443.2011.03576.x
19. Liu, Y., Lin, D., Wu, B., & Zhou, W. (2016). Ketamine abuse potential and use disorder. Brain Research Bulletin, 126, 68–73. https://doi.org/10.1016/j.brainresbull.2016.04.016
20. William, J. M. (2018). Ketamine: A therapeutic paradigm shift. International Journal of Depression and Anxiety, 1, 1–3.
21. Berl, T. (2010). Impact of solute intake on urine flow and water excretion. Kidney International, 78, 738–740. https://doi.org/10.1038/ki.2010.258
22. Bicknell, R. J. (1988). Vasopressin release and control. Trends in Neurosciences, 11(1), 11–16. https://doi.org/10.1016/0166-2236(88)90005-5
23. van Bockxmeer, J. J., Du Toit, S., & Sheehy, K. (2022). Ketamine and vasopressin release: A perioperative challenge. Canadian Journal of Anesthesia, 69, 624–629. https://doi.org/10.1007/s12630-022-02186-0
24. Bisset, G. W. (2001). Vasopressin and its role in the brain. The Journal of Physiology, 537(Pt 1), 1–11. https://doi.org/10.1111/j.1469-7793.2001.0001k.x

25. Kohrs, R., & Durieux, M. E. (1998). Ketamine: Teaching an old drug new tricks. Anesthesia & Analgesia, 87(6), 1393–1400. https://doi.org/10.1213/00000539-199812000-00045
26. Naranjo, C. A., Busto, U., Sellers, E. M., Sandor, P., Ruiz, I., Roberts, E. A., ... & Greenblatt, D. J. (1981). A method for estimating the probability of adverse drug reactions. Clinical Pharmacology & Therapeutics, 30(2), 239–245. https://doi.org/10.1038/clpt.1981.154
27. Cuesta, M., & Thompson, C. J. (2016). SIADH: Diagnosis and management. Clinical Endocrinology (Oxford), 84(5), 664–670. https://doi.org/10.1111/cen.12915
28. Hoorn, E. J., & Zietse, R. (2008). Diagnosis and treatment of hyponatremia: Compilation of the guidelines. Kidney International, 73(7), 798–802. https://doi.org/10.1038/sj.ki.5002717
29. Liamis, G., Filippatos, T. D., & Elisaf, M. S. (2008). Electrolyte disorders associated with the use of antidepressants. American Journal of Kidney Diseases, 52(1), 144–153. https://doi.org/10.1053/j.ajkd.2008.02.297
30. Adrogué, H. J., & Madias, N. E. (2000). Hyponatremia. The New England Journal of Medicine, 342(21), 1581–1589. https://doi.org/10.1056/NEJM200005253422107
31. Peri, A., Giuliani, C., & Tommasi, M. S. (2022). Hyponatremia: From pathophysiology to therapy. Journal of Clinical Medicine, 11(2), 347. https://doi.org/10.3390/jcm11020347
32. Verbalis, J. G., Goldsmith, S. R., Greenberg, A., Schrier, R. W., & Sterns, R. H. (2018). Diagnosis, evaluation, and treatment of hyponatremia: Expert panel recommendations. European Journal of Endocrinology, 178(1), R1–R14. https://doi.org/10.1530/EJE-17-0798