Drug-induced syndrome of inappropriate antidiuretic hormone

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Hypotonic, defined as serum sodium less than 130 mmol/L, is the most common electrolyte disturbance among hospitalized patients. A complication of a variety of diseases, surgical treatments, or drugs, it may be hypertonic, hypotonic, or isotonic in nature.

Antidiuretic hormone (ADH) is also known as arginine vasopressin (AVP). Produced in the posterior pituitary gland in response to an increased plasma sodium concentration, it induces water retention. It increases cellular permeability to water in the distal tubule and collecting duct of the nephron, leading to increased water resorption by the kidney.

The syndrome of inappropriate antidiuretic hormone secretion (SIADH) is characterized by either the sustained release of ADH in the absence of stimuli, or by the enhanced action of ADH on the kidneys. Increased ADH activity impairs the kidney’s ability to dilute urine, resulting in decreased excretion of ingested water and a highly concentrated and decreased volume of urine.

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If fluid intake is not sufficiently reduced in the setting of increased ADH activity, serum hyponatremia and hypotremia will occur. Patients with SIADH will present with normal volume status (euvolemic) because the excess water distributes evenly throughout the body’s fluid compartments. Causes of SIADH include malignant diseases (e.g., carcinoma, lymphomas, sarcomas), pulmonary disorders (e.g., pneumonia, asthma), central nervous system disorders (e.g., meningitis, stroke, head trauma), and a number of medications.

Signs and symptoms

Clinical manifestations of SIADH relate to the degree of hypotonicity. Signs and symptoms of moderate hyponatremia (serum sodium concentration 115–120 mEq/L) include anorexia, nausea, vomiting, muscle weakness, and cramps. Severe hyponatremia (<110 mEq/L) may be characterized by gait disturbances, falls, stupor, tremors, seizures, and, in rare cases, death. Headache, lethargy, disorientation, restlessness, and obtundation are other possible manifestations. Patients typically present with a low plasma osmolality, elevated urine osmolality (>100 mOsm/kg, usually >300 mOsm/kg), a urine sodium concentration above 40 mEq/L, and low blood urea nitrogen and serum uric acid concentration. Plasma creatinine, acid-base, and potassium balance, as well as adrenal and thyroid function, are all typically within normal limits.

In most cases of drug-induced SIADH, patients have mild, asymptomatic hyponatremia that remains undetected. Others will fully recover once diagnosed. However, at least 6 deaths related to hyponatremia induced by ecstasy (methylene-dioxymethamphetamine, or MDMA) have been reported. Mortality has also been associated with cyclophosphamide- and carbamazepine-induced SIADH.

Drugs that can cause SIADH

While a large number of drugs may be associated with SIADH, most suspected cases are not drug-related. The selective serotonin reuptake inhibitors (SSRIs), various chemotherapeutic agents (e.g., cyclophosphamide, cisplatin, vincristine, vinblastine), chlorpropamide, carbamazepine, MDMA, tricyclic antidepressants, and antipsychotics appear to be most strongly associated with SIADH. The incidence of drug-induced SIADH with carbamazepine may be dose-related.

Drug-induced SIADH can occur due to either an increased sensitivity to ADH in the nephron (e.g., cyclophosphamide, chlorpropamide, carbamazepine), or an increase in ADH production centrally (e.g., vinca alkaloids, cyclophosphamide, carbamazepine, antipsychotics, antidepressants). A list of drugs that may cause SIADH is provided in Table 1. Many of these associations are based on as little as one case report.

A review of spontaneous reports of hyponatremia associated with SSRI use found that the median time to onset was 13 days after initiation of therapy, with a range of 3 to 120 days. While the occurrence of hyponatremia with antidepressants appears to be highest during the first few weeks of treatment, the time to onset with antipsychotics seems to be considerably longer. Risk
factors for SSRI-induced SIADH include advanced age, female gender, concomitant diuretics, hyperkalemia, baseline hyponatremia, and lower body mass index.

Management
The only definitive treatment for drug-induced SIADH is removal of the offending agent. Most cases resolve promptly upon drug discontinuation. Management should be guided by the severity and duration of hyponatremia and its symptoms.1 Typically in drug-induced SIADH, the hyponatremia will be chronic and asymptomatic. In these instances, water should be restricted (500–1000 mL/day), and this measure alone may be adequate. It may be necessary to add furosemide to increase the excretion of free water and if needed, replace salt and volume by administering 0.9% sodium chloride intravenously.4 For severely hyponatremic and symptomatic patients, administration of hypertonic saline (3%) may be appropriate. Serum sodium should not increase by more than 1 to 2 mmol/L per hour or 8 to 10 mmol/L in the first 24 hours, as there is a risk of osmotic demyelination.1

In cases in which removal of the offending agent is not possible, treatment options include demeclocycline (a tetracycline derivative), oral urea, and lithium. Demeclocycline, currently available through Health Canada’s Special Access Program, reduces urine osmolality and increases serum sodium levels; however, the risk of nephrotoxicity and variable efficacy may limit its use.1 Urea (30 g po daily) increases urine production by acting as an osmotic diuretic, but it is generally not well tolerated.17 The crystals may be mixed with 10 mL of Maalox and dissolved in 100 mL of water to reduce gastrointestinal upset.7,11 The unpleasant taste can be masked by using juices or carbonated beverages, or by mixing the crystals with jelly or jam.11 Lithium has also been used with some success, but it is currently not recommended due to the potential for adverse events and a lack of evidence supporting its use.1,5

With respect to SSRI-induced SIADH, cross-sensitivity among agents has been reported, but published data are scarce.4,12 Caution should be used if any SSRI is to be re-initiated.12 Monitoring of serum sodium concentrations at baseline and 1 to 2 weeks after initiation of SSRIs may be warranted in individuals at risk of SIADH.13 For elderly patients taking an SSRI and presenting with sudden or unexplained mental status changes (e.g., delirium, lethargy, confusion) or nausea, measurement of serum sodium concentration is advised.12-13

Summary
Many medications have been associated with SIADH; however, the actual incidence of drug-induced SIADH is estimated to be very low.4 Symptoms of SIADH are linked to the degree of hyponatremia, and most drug-induced cases are mild in nature.1,4
Removal of the offending agent is the most effective treatment. In the case of SSRIs, extreme caution should be used when switching to another agent of that class. Other treatment alternatives include demeclocycline, urea, and lithium. While it is important to be aware of this possible adverse effect, it is probably not necessary to counsel all patients on the risk of SIADH.4

This article was written by Erika Jones, a pharmacist at The Ottawa Hospital, and reviewed by Norma Lynn Pearson and Mirella Giudice with the Ottawa Valley Regional Drug Information Service at The Ottawa Hospital.

References