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SYNDROME OF INAPPROPRIATE ANTIDIURETIC HORMONE RELEASE

Lodging a Complaint . . . . . Level I

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INSTRUCTOR'S GUIDE TO CHANGES IN THIS EDITION

CASEBOOK

Patient Presentation

- Modified patient case presentation; patient is 73 years old and has a history of depression treated with fluoxetine. Minor changers to PMH, FH, SH, ROS, PE, and laboratory tests.

Clinical Course

- Revised to exclude use of ecstasy prior to the auto accident.

INSTRUCTOR'S GUIDE

Problem Identification

- Fluoxetine added as a possible medication-related cause of syndrome of inappropriate antidiuretic hormone (SIADH).

Desired Outcome

- Revised to add information on managing hyponatremia in symptomatic patients.

Therapeutic Alternatives

- Information added on tolvaptan (Samsca), another FDA-approved vasopressin receptor antagonist.
- Information added on the investigational vasopressin receptor antagonist lixivaptan.

Optimal Plan

- Revised calculations and recommendations for administration of 3% saline solution in this symptomatic patient.

Patient Education

- Deleted information on demeclocycline, since patients who recover from acute hyponatremia/SIADH may not require subsequent therapy.

Follow-Up Questions

- Question added about whether the patient should continue fluoxetine on discharge.

References

- Updated and revised; four new references added and three references deleted.

CASE SUMMARY

A 73-year-old man presents to the emergency department with altered mental status following a car accident 3 days ago. He sustained a head injury but refused to go to the hospital at that time. Per reports from his wife who accompanied him to the emergency department, the patient has been acting confused and disoriented since the accident, with worsening symptoms in the last 24 hours. Laboratory evaluation reveals hyponatremia (serum sodium 112 mEq/L), high urinary sodium concentration, low serum uric acid level, and normal renal function findings that are consistent with SIADH. The cause of SIADH in this patient is probably due to head trauma, but students should also consider the possibility of drug-induced SIADH. In this patient, that would include the use of fluoxetine, a selective serotonin reuptake inhibitor (SSRI). The serum sodium concentration should be gradually normalized over the next 2–3 days. Fluid restriction, hypertonic (3%) saline, and furosemide may be required acutely. Treatment with vasopressin receptor antagonists is not standard of care due to the lack of information and experience. Patients with chronic SIADH may be treated with demeclocycline; however, this is not indicated in acute treatment. Students should understand that slow repletion of sodium is necessary to prevent the osmotic demyelination syndrome. Changes in neurologic function should be assessed frequently during the recovery period.

QUESTIONS

Problem Identification

1.a. Create a list of the patient's drug therapy problems.

- Hyponatremia apparently caused by SIADH, which will require sodium supplementation and perhaps other treatment
- Hypokalemia that will require potassium supplementation

1.b. What information (signs, symptoms, laboratory values) indicates the presence or severity of SIADH as the cause of his hyponatremia?

- Hyponatremia is defined as serum sodium concentration <135 mEq/L. Concentrations <110 mEq/L have been associated with an 8% mortality rate.[1] In addition, the rapid decline in mental status in this patient indicates hyponatremic encephalopathy and thus severe hyponatremia.
- Serum osmolality is beneficial in identifying the cause of the hyponatremia. Increases in serum osmolality are seen with hyperglycemia. Hyperglycemia is associated with a 1.6–2.4 mEq/L decrease in serum sodium, causing translocational hyponatremia.[2] Because this patient does not have hyperglycemia, this is not the cause of his hyponatremia.
- To identify SIADH in a patient with hyponatremia, the clinician must determine the patient's extracellular fluid status. Hyponatremic patients may be *hypovolemic* (as a result of diuretic use or dehydration resulting from vomiting or diarrhea), *hypervolemic* (associated with edema or ascites), or *isovolemic* (refer to the textbook chapter related to sodium and water balance for a discussion of the etiologies of hyponatremia). Based on the patient's presentation, he does not appear to be hypervolemic or hypovolemic and therefore may be classified as having isovolemic hyponatremia.

- The causes of isovolemic hyponatremia include glucocorticoid deficiency, severe hypothyroidism, psychogenic polydipsia (excessive water drinking), postoperative hyponatremia, and SIADH. Glucocorticoid deficiency was not thoroughly assessed in this patient, but his clinical picture is not consistent with this diagnosis. He has a normal TSH concentration and no history of excessive water drinking or recent surgery.
- SIADH is associated with hyponatremia with hypotonicity of plasma, increased renal sodium excretion (urinary sodium concentrations >20 mEq/L), high urinary osmolality relative to serum osmolality, absence of edema or evidence of volume depletion, low uric acid concentrations, and normal renal and adrenal function.[3,4] Therefore, SIADH is the most likely diagnosis.
- SIADH is strongly associated with central nervous system disorders including head trauma, which this patient has experienced.[4]

1.c. Could any of the patient's problems have been caused by drug therapy?

- This patient has been taking fluoxetine daily for the last 6 years. SSRIs (particularly fluoxetine) have been associated with the development of SIADH. The risk is highest within the first month of therapy.[5] Most patients experience hyponatremia within 13 days of starting SSRI therapy, with 66% presenting within 30 days of therapy.[6] Since this patient has been on therapy for 6 years, it is unlikely that the current sodium imbalance is due to fluoxetine.
- Albuterol has not been associated with SIADH.
- Many drugs have been implicated in causing hyponatremia. However, not all drugs that cause hyponatremia cause SIADH. Thiazide diuretics are commonly associated with hyponatremia, but it is the hypovolemic, hypotonic type, not the isovolemic, isotonic type seen with SIADH. Opioids, phenothiazines, chlorpropamide, nonsteroidal anti-inflammatory drugs, carbamazepine, tricyclic antidepressants, clofibrate, vincristine, cyclophosphamide, and oxytocin have caused SIADH by either increasing antidiuretic hormone (ADH) release or sensitizing the kidney to the effects of ADH.[3,4]

Desired Outcome

2. What are the goals of pharmacotherapy in this case?

- Normalize serum electrolyte concentrations over the next 48–72 hours.
- The serum sodium concentration should not increase faster than 0.5 mEq/L/h or by 12 mEq/L in the first 24 hours to minimize the likelihood of neurologic damage. In symptomatic patients, increases up to 1.5 mEq/L/h may be necessary for a short duration, 2–4 hours (for a total of 3–6 mEq/L); however, the total of 12 mEq/L in the first 24 hours should still be maintained.
- Maintain normal serum electrolytes.

Therapeutic Alternatives

3.a. What nondrug therapies might be useful for this patient?

- Supportive therapy in an intensive care unit should be provided for patients with severe hyponatremic encephalopathy. Frequent monitoring of cardiac, pulmonary, neurologic, and volume status is imperative. Ventilator support care should be provided as necessary.
- Water restriction (usually 1–1.2 L per day) should be emphasized in isovolemic patients with hyponatremia. Fluid restricting patients more than 1 L per day is difficult because patients require about 500 mL per day to achieve obligatory urine output.
- Underlying conditions (e.g., hypothyroidism) should be treated, and possible offending medications should be evaluated for appropriateness.
- Patients with a history of psychogenic polydipsia should not have free access to water.

3.b. What pharmacotherapeutic alternatives are available for the treatment of hyponatremia?

- *Hypertonic saline (3% sodium chloride)* should be given to patients with symptomatic isovolemic hyponatremia or serum sodium concentrations below 120 mEq/L. Normal saline has a limited role in the management of isovolemic hyponatremia/SIADH because the sodium may be excreted rapidly resulting in retention of "free" water.[3]
- *Furosemide* 40 mg IV every 6 hours may be added to hypertonic saline to increase the excretion of free water or if volume overload occurs, especially in patients with urine osmolalities exceeding 300 mOsm/kg.
- *Demeclocycline* 600–1,200 mg per day po may be given to patients with chronic SIADH if fluid restriction alone does not control the hyponatremia. It should not be considered for the acute management of SIADH because of its delayed onset of action (3–6 days).
- *Lithium carbonate* has also been used, but its toxicity and somewhat unpredictable response in SIADH have made demeclocycline the drug of choice. Both agents cause diabetes insipidus (insensitivity of the kidney to ADH) over the course of several days. The net result is an increase in serum sodium concentration and tonicity.
- *Vasopressin receptor antagonists* are a new class of drugs that promote the excretion of free water (aquaresis) and may be beneficial in hyponatremia.
  - ✓ *Conivaptan (Vaprisol)* is a vasopressin antagonist with activity at the V_{1A} and V_2 receptors. It has an FDA-approved indication for the treatment of euvolemic hyponatremia (e.g., SIADH, or in the setting of hypothyroidism, adrenal insufficiency, pulmonary disorders) in hospitalized patients. Conivaptan must be given intravenously through a large vein, and the infusion site should be rotated every 24 hours to minimize the risk of vascular irritation. A 20-mg loading dose should be given IV over 30 minutes on day 1 followed by a continuous IV infusion of 20 mg over the next 24 hours. The continuous infusion can be titrated up to 40 mg if the sodium concentration is not rising at a sufficient rate. The infusion may be continued for a total of 96 hours. Conivaptan has been shown to significantly increase free water excretion and help normalize serum sodium concentrations. It is expected to increase sodium concentrations an average of 6 mEq/L from baseline or to a normal serum sodium concentration (≥135 mEq/L) over the duration of treatment. The most common adverse effects are infusion site reactions, including pain and phlebitis. Other adverse effects include thirst, headache, and hypokalemia. Serum sodium concentrations should be monitored during therapy to prevent osmotic demyelination syndrome. The serum sodium concentration should not increase faster than 0.5 mEq/L/h or by 12 mEq/L in the first 24 hours. Conivaptan is contraindicated in patients with hypovolemic hyponatremia and in those who have hypersensitivity to any of its components. It is a substrate and an inhibitor of CYP3A4;

therefore, concomitant use of conivaptan with other drugs metabolized primarily by CYP3A4 should be monitored closely, or the combination should be avoided. The co-administration of conivaptan with potent CYP3A4 inhibitors, such as ketoconazole, itraconazole, clarithromycin, ritonavir, and indinavir, is contraindicated. The safety of conivaptan in hyponatremic patients with underlying heart failure has not been established.[7] Estimated cost for a treatment dose consisting of one 20-mg loading dose followed by a 20-mg continuous infusion for 4 days is approximately $1,500.

✓ *Tolvaptan* (*Samsca*) is a selective, competitive arginine vasopressin receptor-2 antagonist with FDA approval for the treatment of "clinically significant" hypervolemic or euvolemic hyponatremia. Tolvaptan starting dose is 15 mg once daily. The dose may be increased to 30 mg once daily if after at least 24 hours a greater increase in the serum sodium concentration is necessary. An additional increase to 60 mg once daily may be used if again, after 24 hours of the 30-mg dosage, a still greater increase in serum sodium concentration is desired. Tolvaptan must begin or resume only in a hospital setting where close monitoring of the patient's serum sodium concentrations can be performed, and patient counseling including a review of the product's medication guide must be conducted with every patient receiving tolvaptan therapy. Common adverse events associated with tolvaptan include thirst, dry mouth, weakness, constipation, hyperglycemia, and polyuria. Tolvaptan is only indicated for the treatment of symptomatic hypervolemic or euvolemic hyponatremia not responsive to fluid restriction. It is contraindicated in patients requiring an urgent need to acutely raise sodium, patients unable to sense or respond appropriately to thirst, patients with hypovolemic hyponatremia, patients taking a strong cytochrome p-450 isoenzyme 3A inhibitor who cannot stop that therapy, and patients who are not forming and excreting urine.[8]

✓ *Lixivaptan* is an orally active V_2-specific vasopressin receptor antagonist in Phase III clinical trials for the treatment of hyponatremia. It has been studied in SIADH, congestive heart failure, and cirrhosis.[7]

Lack of research and experience precludes recommending these drugs as first-line agents for acute or chronic SIADH. However, conivaptan and tolvaptan may be appropriate alternatives when conventional treatments are ineffective, difficult to tolerate, or contraindicated.

Optimal Plan

4. What drug, dosage form, dose, schedule, and duration of therapy are most appropriate for initial treatment of this patient?

- In general, to prevent possible neurologic damage, the serum sodium concentration should not increase faster than 0.5 mEq/L/h or by 12 mEq/L in the first 24 hours.
- Using the calculations from the textbook chapter related to sodium and water balance, 1 L of 3% saline should increase this patient's serum sodium concentration by 8.3 mEq. Therefore, the patient should receive IV hypertonic (3%) saline at a rate not greater than 60 mL/h (maximum) monitoring the patient's serum sodium concentration every 2–4 hours. Because the patient is symptomatic, increasing the serum sodium concentration by 1.5 mEq/L/h over the first 2–4 hours is acceptable; therefore, an alternative regimen would be 180 mL/h for the first 2–4 hours, followed by an infusion rate of approximately 36–49 mL/h for the next 22 or 20 hours, respectively.
- The duration of hypertonic saline therapy depends on the severity of hyponatremia and the rate of correction. Infusion may be discontinued when serum sodium concentrations reach 120 mEq/L and symptoms resolve.
- Free water restriction to 1,000 mL per day is also indicated.
- Furosemide in initial doses of 40 mg IV every 6 hours may be added.
- Demeclocycline and lithium have no role in the treatment of acute SIADH because they require several days to take effect.
- Patients with stable asymptomatic hyponatremia (usually >120 mEq/L) may not require any treatment.

Outcome Evaluation

5. What clinical and laboratory parameters are necessary to evaluate the therapy for achievement of the desired therapeutic outcome and to detect or prevent adverse effects?

- Initially, serum sodium concentrations should be measured every 2–4 hours during treatment. The increase in serum sodium concentration should be kept at 0.5 mEq/L/h for the first 24 hours. Too rapid repletion of sodium is associated with osmotic demyelination syndrome (or central pontine myelinolysis), which is thought to be caused by rapid fluid and electrolyte shifts within the central nervous system. This syndrome is manifested as quadriplegia, pseudobulbar palsy, mutism, swallowing difficulties, and other neurologic symptoms, and even death.
- For this reason, patients should be examined for changes in neurologic function. These parameters include weakness, paralysis, inability to speak, changes in mental status or sensation, and choking or aspiration. Typical symptoms occur within 5 days of repletion of sodium.[2]
- Urine osmolality should be repeated every 4–6 hours over the first day.
- Other electrolytes, including potassium, should be repleted as necessary over the next 48 hours.

Patient Education

6. What information should be provided to the patient to enhance compliance, to ensure successful therapy, and to minimize adverse effects?

- Patients who have recovered from acute hyponatremia/SIADH may not require any additional therapy.

■ FOLLOW-UP QUESTION

1. Is discontinuation of the patient's SSRI warranted?

- It is difficult to determine whether this patient's SIADH was caused by the head injury or use of fluoxetine. However, the treatment for SIADH would not change in either case. Treatment for hyponatremia is determined by the cause, but treatment for SIADH is not.
- SSRI-induced hyponatremia has been widely discussed in the literature. A review published in 2006 reported the overall incidence to be from 0.5% to 32%.[8] Risk factors for developing hyponatremia include:
  - ✓ Older age
  - ✓ Female gender
  - ✓ Concomitant use of diuretics
  - ✓ Low body weight
  - ✓ Lower baseline serum sodium

- The median onset of hyponatremia reported is 13 days after the start of treatment.[9]
- One possible mechanism is induction of ADH release or increased responsiveness to ADH. SSRIs may also inhibit the reuptake of norepinephrine to a small degree; this could lead to increased release of ADH.[9]
- Fluoxetine should be continued since this patient has been taking it for 6 years and was previously without complaint. His hyponatremia was likely due to the head injury sustained after the motor vehicle accident. Correction of the hyponatremia and close monitoring are warranted.

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