JAMA Diagnostic Test Interpretation

Hypernatremia

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A healthy 36-year-old man underwent transsphenoidal resection of a pituitary macroadenoma, which had been discovered incidentally on brain magnetic resonance imaging. In the immediate postoperative period, he received a 0.9% saline infusion as part of routine postoperative treatment. Within 30 minutes of arrival in the recovery room, he developed persistent, large-volume urine output (400 mL/h). Blood testing performed 6 hours after the operation showed a sodium value of 148 mEq/L, increased from a baseline level of 138 mEq/L. Complete laboratory results are found in the **Table**.

WHAT WOULD YOU DO NEXT?

A. Administer desmopressin

B. Infuse lactated Ringer solution

C. Measure arginine vasopressin levels

D. Prescribe tolvaptan

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Table. Patient's Laboratory Test Results

Laboratory test	Patient's value	Reference range
Preoperative plasma		
Sodium, mEq/L	138	136-145
Postoperative plasma		
Sodium, mEq/L	148	136-145
Potassium, mEq/L	3.7	3.4-5.0
Bicarbonate, mEq/L	26	21-27
Glucose, mg/dL	90	60-99
Calcium, mg/dL	9.5	8.6-10.3
Blood urea nitrogen, mg/dL	12	6-24
Creatinine, mg/dL	0.7	0.6-1.1
Urine		
Flow rate, mL/h	400	Varies
Osmolality, mOsm/kg H_2O	91	50-1200
Urine sodium, mEq/L	30	Varies
Urine potassium, mEq/L	9	Varies

SI conversion factors: To convert blood urea nitrogen to mmol/L, multiply by 0.357; creatinine to μmol/L, multiply by 88.4; glucose to mmol/L, multiply by 0.0555; calcium to mmol/L, multiply by 0.2495.

Answer

A. Administer desmopressin

Test Characteristics

Hypernatremia is defined as plasma sodium concentration greater than 145 mEq/L and represents an increase in the quantity of sodium relative to the volume of water in the extracellular fluid.[1] An increase in plasma sodium level is sensed by osmoreceptors in the hypothalamus, causing release of arginine vasopressin (AVP) from the posterior pituitary and stimulating thirst. AVP binds to the vasopressin 2 receptors in the kidney collecting ducts, leading water to flow from the tubular lumen to the surrounding interstitium, producing a small volume of concentrated urine. Hypernatremia resolves with ingestion of water and can persist if an individual has a defect in sensing thirst, an inability to obtain water, or both.[1]

Hypernatremia is most often caused by a loss of hypotonic fluids and results in a hypovolemic or euvolemic state, depending on the amount of sodium intake (**Figure**). Extrakidney loss of hypotonic fluid (eg, sweating, hyperventilation, vomiting, osmotic diarrhea) causes excretion of a low volume of concentrated urine (urine output <30 mL/h with urine osmolality >600 mOsm/kg H_2O).[3] Kidney loss of hypotonic fluid is due to a water diuresis caused by diabetes insipidus (DI), which is associated with urine osmolality less than 300 mOsm/kg H_2O, or an osmotic diuresis due to hyperglycemia, mannitol, or urea, which typically results in urine osmolality of 400 to 600 mOsm/kg H_2O.[3]

Less commonly, hypernatremia may be caused by a net gain of hypertonic fluids, which leads to a hypervolemic state (Figure). Examples include infusion of hypertonic sodium bicarbonate intravenous fluids, salt poisoning in children, massive salt ingestion,[4] and replacement of hypotonic fluids losses with isotonic saline, which frequently occurs in critically ill patients in the intensive care unit.[5]

Hypernatremia results from decreased AVP production in the hypothalamus or failure of the pituitary to secrete AVP (central DI), excess release of a vasopressinase from the placenta (gestational DI), or kidney resistance to the action of AVP (nephrogenic DI). Central DI, which has a prevalence of 3 in 100 000 individuals,[6] may result from tumors invading the hypothalamic-pituitary-axis (HPA), infiltrative diseases of the HPA (such as sarcoidosis), neurosurgery, or head trauma and is idiopathic in approximately 30% of cases.[7] Nephrogenic DI is mostly commonly caused by lithium, occurring in 20% to 40% of long-term lithium users,[7] but may also be due to electrolyte disorders (such as hypercalcemia or hypokalemia).[7]

Central and nephrogenic DI can be differentiated by the effect that administration of desmopressin has on urine osmolality. Individuals with central DI develop concentrated urine after receiving

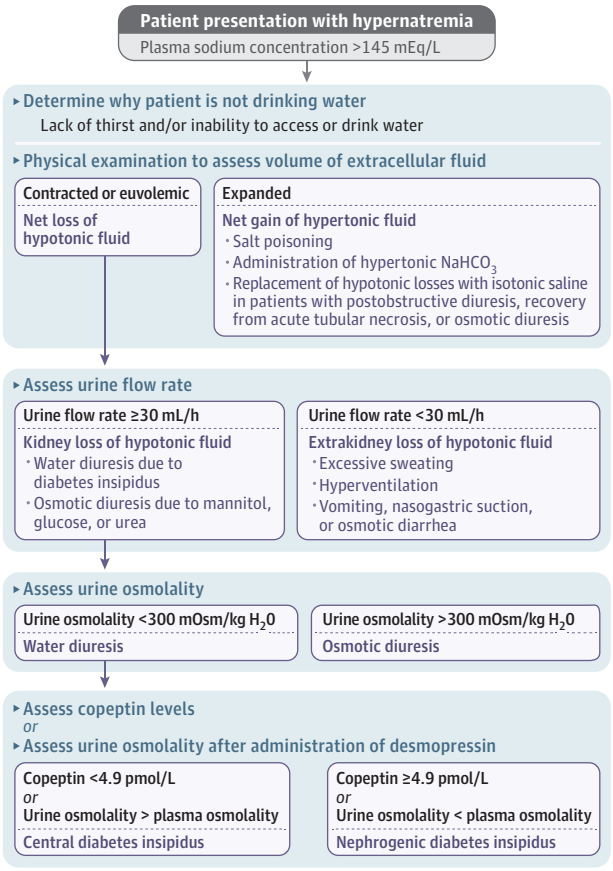

Figure. This approach has not been evaluated or validated in clinical studies. There are limitations of physical examination in the assessment of extracellular fluid.[2] If available, plasma copeptin levels can be measured as an alternative to the administration of desmopressin to determine the cause of the water diuresis. Chronic polyuria may result in washout of the medullary concentration gradient; therefore, urine osmolality after desmopressin administration in a patient with central diabetes insipidus may be lower than expected, but should be higher than plasma osmolality.[3]

desmopressin, whereas urine osmolality does not increase in those with nephrogenic DI due to kidney resistance to desmopressin.

According to January 2022 Medicare data, national reimbursement limits were $4.81 for plasma sodium testing and $6.82 for urine osmolality testing.

Application of Test Results to the Patient

The development of a high urine flow rate with dilute urine (urine osmolality of 91 mOsm/kg H_2O) after resection of a pituitary macroadenoma made central DI the most likely cause of this patient's hypernatremia. However, sodium from the postoperative 0.9% saline infusion he received may have partially contributed to the hypernatremia.

What Are Alternative Diagnostic Testing Approaches?

Plasma sodium is the only laboratory measure for detecting hypernatremia. When DI is considered a likely cause of hypernatremia, plasma copeptin, the C-terminal glycoprotein moiety of the AVP prohormone, serves as a reliable marker of plasma AVP and can help differentiate between nephrogenic and central DI.[8,9]

Patient Outcome

When hypernatremia was identified on postoperative blood testing results, the 0.9% saline infusion was stopped and an infusion of 5% dextrose was initiated. The diagnosis of central DI was confirmed with administration of 2 µg of intravenous desmopressin (a synthetic analogue of AVP), which increased urine osmolality from 91 to 432 mOsm/kg H_2O within 1 hour. The patient received a daily dose of desmopressin until hospital day 4, when he was prescribed once-daily 60-µg oral desmopressin acetate, and was discharged home on hospital day 5. One year later, he continued receiving daily desmopressin treatment and had a normal plasma sodium level.

Clinical Bottom Line

- Hypernatremia is most commonly due to loss of hypotonic fluid from the skin (diaphoresis), lungs (hyperventilation), gastrointestinal tract (vomiting or osmotic diarrhea), or the kidney (due to diabetes insipidus [DI] or osmotic diuresis).
- Central DI is caused by decreased arginine vasopressin (AVP) production or secretion in the brain.
- Nephrogenic DI occurs when the kidney demonstrates resistance to the urinary concentrating effects of AVP.
- Central DI and nephrogenic DI can be differentiated by the effect that desmopressin has on urine osmolality or by measurement of plasma copeptin, the C-terminal glycoprotein moiety of the AVP prohormone.

ARTICLE INFORMATION

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