A Suspected Case of Carbamazepine-Induced Hyponatremia

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Carbamazepine has been associated with several potentially serious side effects, among which are bone marrow suppression, liver and renal dysfunction, ocular lens opacities, leukopenia, rashes, gastrointestinal distress, and a condition resembling the syndrome of inappropriate secretion of antidiuretic hormone (SIADH).

The following report describes a suspected case of a SIADH-like syndrome in an elderly woman receiving carbamazepine for the management of herpes zoster pain. A brief review of carbamazepine-induced hyponatremia and its potential causes and treatment are described.

CASE REPORT

N.B. is a 69-year-old woman who was admitted to the hospital on March 17, 1989, with disseminated herpes zoster, nausea, dehydration, and severe pain. Much of the patient's severe pain arose from trigeminal nerve involvement.

A neurology consultant recommended that carbamazepine be initiated to help control the pain and obviate postherpetic neuralgia. She was begun on oral carbamazepine, 300 mg daily, on March 20, 1989. This dosage was increased to 500 mg 1 day later on the day of discharge. Serum sodium at the time of discharge was 133 mmol/L (133 mEq/L). On March 22, 1989, she took her full dose of carbamazepine, 300 mg twice a day. That day she experienced an episode of mild nausea and vomiting. She was seen in the Family Practice Center on the next day. Her blood pressure was 200/92 mm Hg; orthostasis was not assessed. Her carbamazepine dose was decreased to 200 mg twice a day.

She was again seen in the Family Practice Center, on March 27, 1989. She still complained of continued nausea, mild ataxia, and disequilibrium. On physical examination her oral mucosa was found to be moist. She was mildly orthostatic with no change in pulse. Her urine specific gravity was 1.010. Her carbamazepine level was not determined at this time, and the drug was stopped.

Two days later she reported an improved appetite, greatly decreased nausea, and no further disequilibrium.

On March 30, 1989, she was admitted to the hospital following a syncopal episode. Prescription medication at admission included a combination of 25 mg of hydrochlorothiazide and 50 mg of triamterane daily, which was subsequently discontinued. Her serum sodium at admission was 120 mmol/L (120 mEq/L). Additionally, her potassium was 2.9 mmol/L (2.9 mEq/L), chloride was 81 mmol/L (81 mEq/L), and carbon dioxide was 29 mmol/L (29 mEq/L). Blood urea nitrogen and creatinine were normal. Serum carbamazepine level was less than 4 μmol/L (1 μg/mL). She was mildly orthostatic.

The patient was placed on fluid restriction. Initial serum and urine osmolalities were 262 mmol/kg (262 mOsm/kg) and 265 mmol/kg (265 mOsm/kg), respectively. Urine specific gravity was 1.008. Repeat values on the next day were 267 mmol/kg (267 mOsm/kg) and 340 mmol/kg (340 mOsm/kg), respectively. Her urine sodium level was less than 10 mmol/L (10 mEq/L). Following approximately 4 days of fluid restriction, her serum sodium had increased to 131 mmol/L (131 mEq/L). Serum potassium and chloride also returned to normal.

On the day of discharge, April 3, 1989, she was no longer dizzy and could walk in the hallway, although some minimal ataxia was still present. Serum sodium at discharge was 131 mmol/L (131 mEq/L). Repeat electrolyte values on April 12, 1989, were normal.

continued on page 666

Submitted, revised, June 5, 1990.

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continued from page 664

DISCUSSION

Carbamazepine is usually well tolerated, although a variety of adverse effects have been reported. Of particular interest is the drug's ability to cause the syndrome of inappropriate secretion of antidiuretic hormone (SIADH). The exact incidence and predisposing factors are not well understood.[1–7]

Drugs that cause SIADH do so in one of two ways. Either the drug (eg, carbamazepine) stimulates the release of antidiuretic hormone (vasopressin) from the posterior pituitary gland, or it increases the sensitivity of the renal collecting ducts to the action of the hormone. Vasopressin is released whenever serum osmolality is increased or when there is extracellular fluid volume depletion (independent of plasma osmolality).[8] Stress, nausea, volume depletion, hypoxia, pain, and hypotension can also act as stimulants to the release of vasopressin. Such factors must be ruled out before a pharmacologic agent can be implicated in precipitating SIADH.[9]

When vasopressin is secreted in excess, or its pharmacologic actions are exaggerated, the kidney retains an increased amount of free water, which expands all water compartments in the body. This expansion increases glomerular filtration rate, suppresses the renin-angiotensin system, and leads to enhanced renal sodium excretion.[9] Patients exhibiting SIADH have no evidence of volume depletion, urine osmolality is inappropriately high, urine sodium excretion is usually greater than 20 mmol/L (20 mEq/L), and there is no evidence of inherent heart, kidney, or adrenal disease.[1] Serum sodium and uric acid also fall below the normal range.[9]

Symptoms result from hypotonicity of body fluids and electrolyte disturbances. The rapidity with which this clinical syndrome occurs will also determine the nature of patient symptoms.[9] Common patient complaints include confusion, dizziness, fatigue, and disorientation.[1] Other symptoms can include gastrointestinal distress, personality changes, seizures, coma, and death.[9]

N.B. was suspected of having carbamazepine-induced SIADH. She experienced episodes of nausea, vomiting, and ataxia 1 week following discharge from the hospital. While at home, she could not tolerate solid food, and she was encouraged by her family to drink fluids. It is interesting that carbamazepine-induced SIADH can occur in polydipsic patients.[4,5] At readmission to the hospital, her blood chemistry determinations were also consistent with SIADH. The finding of hypokalemia may have resulted from the concomitant administration of a diuretic and her poor oral intake before hospitalization. Diuretic therapy may be a predisposing factor for the development of carbamazepine-induced SIADH.[1,6] Interestingly, the risk of carbamazepine-induced hyponatremia has been associated with increased age (>30 years) and serum drug levels greater than 25 mmol/L (6 μg/mL). N.B. was older, although the serum carbamazepine level was less than 4 mmol/L (1 μg/mL) at admission, reflecting drug discontinuation several days earlier. It can only be assumed that her drug level was at least within the therapeutic range. Older patients with cardiovascular disease may also be at increased risk for developing drug-induced SIADH.[1] N.B. did have a history of congestive heart failure.

Admission serum and urine osmolalities were 262 mmol/kg and 265 mmol/kg (262 and 265 mOsm/kg), respectively. Repeat values were 267 and 340 mmol/L (267 and 340 mOsm/kg), respectively, a finding more consistent with SIADH. The urine sodium level determined 1 day following admission (<10 mmol/L [10 mEq/L]) is inconsistent with SIADH; however, the patient was previously begun on fluid restriction, and carbamazepine had been stopped several days earlier.

N.B. had borderline low serum sodium, (133 mmol/L [133 mEq/L]) before the March 20 initiation of carbamazepine. A recent study suggests that patients with low normal serum sodium may be predisposed to developing carbamazepine-induced SIADH,[7] and that such patients warrant careful initiation and close monitoring of the drug.

N.B. exhibited many of the features of drug-induced SIADH. The inconsistencies found may reflect the discontinuation of the drug before admission, allowing time for the metabolic abnormalities to begin correcting. Her age, history of congestive heart failure, fluid intake, carbamazepine dose, and diuretic use could have all predisposed her to a greater risk of SIADH. Rechallenge with the drug was not attempted. Plasma vasopressin concentrations were also not obtained, nor was a water load test attempted. The results of these tests could have been used to confirm the presumptive diagnosis of drug-induced SIADH.[9]

This patient was managed conservatively with fluid restriction. Total water intake should not exceed 1000 mL/d.[1,9] Serum osmolality and electrolytes will increase, and the central nervous system effects will improve. Furosemide and hypertonic saline can also be used when rapid correction is necessary.[10,11] Patients unresponsive to simple fluid restriction may benefit from the administration of lithium carbonate, demeclocycline, or urea.[9,11]

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