CLINICAL CASE REPORTS

Nonsteroidal Anti-Inflammatory Drug-Induced Severe Hyponatremia

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Summary. *Hyponatremia (serum sodium level, <135 mmol/L) occasionally may develop in the course of treatment with nonsteroidal anti-inflammatory drugs, which are usually used in daily clinical practice. Nonsteroidal anti-inflammatory drugs diminish the normal inhibitory effect of prostaglandins on the activity of antidiuretic hormone and can therefore reduce free water excretion, leading to water retention and induction or exacerbation of hyponatremia. In this report, we present a case of hyponatremia in a 78-year-old man who had received meloxicam, a nonsteroidal anti-inflammatory drug.*

Introduction

Severe hyponatremia is a rare side effect caused by nonsteroidal anti-inflammatory drugs (NSAIDs) and can be associated with serious effects on the central nervous system (1). Neurological symptoms due to hyponatremia are related a very low serum sodium level as well as a rapid change in the serum sodium concentration. Nausea and malaise may be the earliest symptoms in patients with mild hyponatremia (serum sodium concentration, < 130 meq/L) (1). However, more serious neurological symptoms, such as headache, lethargy, seizures, coma, and respiratory arrest, can occur if the serum sodium concentration falls below 115 to 120 meq/L (1). It is thought that the mentioned complications due to hyponatremia can generally be induced by any of the NSAIDs, although indomethacin is considered as most potent. Herein, we report on a 78-year-old man with hyponatremia caused by the use of meloxicam (a NSAID), which resulted in altered consciousness. To the best of our knowledge, this is the first report that demonstrates severe hyponatremia caused by meloxicam.

Case Report

A 78-year-old man was admitted to the emergency service with headache, nausea, and slurred speech followed by impaired consciousness, which occurred within the last 24 hours. His past medical history revealed the use of meloxicam at a dosage of 15 mg twice daily for 5 days to relieve chronic back pain before the onset of symptoms. On the other hand, his past medical history was unremarkable,

and he had no dietary restriction for sodium, no history of heavy exercise, polydipsia, or concomitant use of any other medication.

On the physical examination at admission, the patient was slim with normal blood pressure, pulse frequency, and body temperature. The findings from the neurological examination were normal except for the presence of apathy and altered cooperation and orientation. Volume status was determined clinically and was considered as euvolemic as no evidence of dehydration, e.g., fast and weak pulse, dry mucous membranes, poor capillary refill, decreased skin turgor, and orthostatic hypotension, and no evidence of hypervolemia, e.g., the presence of extremity or lung edema and elevated jugular venous pressure, was found. Other findings from the physical examination were found to be normal.

The laboratory findings were as follows: sodium, 114 mmol/L (reference range, 136–145 mmol/L); potassium, 3.9 mmol/L (3.5–4.5 mmol/L); chloride, 102 mmol/L (98–106 mmol/L); blood urea nitrogen, 22 mg/dL (7–28 mg/dL); creatinine, 1.0 mg/dL (0.2–1.2 mg/dL); glucose, 105 mg/dL (70–110 mg/dL); uric acid, 3.2 mg/dL (3.6–7.7 mg/dL); and calculated serum osmolarity, 242 mosm/kg (285–295 mosm/kg). Urine sodium and urine osmolarity were 139 mEq/L and 364 mosm/kg, respectively. The results of computed tomography of the head and electroencephalography were normal. The results of serum cortisol level and thyroid function tests were within the reference limits.

On the day of admission, meloxicam was discontinued. As the patient had symptomatic hyponatremia, 3% saline infusion at a rate of 100 mL per hour was initiated in order to increase a serum sodium level to more than 120 mmol/L. Approximately 4 hours after the initiation of 3% saline infu-

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sion, the patient's sodium concentration increased to 119 mmol/L, and his mental status improved. At that time, an infusion rate of 3% saline was decreased to 40 mL per hour. After the serum sodium concentration increased to 130 mmol/L, 3% saline infusion was discontinued, and fluid intake was restricted to 1500 mL per day. The patient's mental status was completely restored at 36 hours after the admission. Five days after the admission, the serum sodium level was 137 mmoL/L, and the patient was subsequently discharged. One week after the discharge, the serum sodium concentration was 140 mmoL/L.

Discussion

Based on clinical euvolemia in association with hyponatremia with a high urine sodium level and urine osmolarity, and relative hypouricemia with normal renal, thyroid, and adrenal functions, an acute symptomatic syndrome of the inappropriate secretion of antidiuretic hormone (SIADH) was diagnosed in our patient. In order to exclude any other cause of SIADH, additional investigations, such as chest radiography, pulmonary function tests, abdominal ultrasound, and echocardiography, were performed. As the additional investigations revealed no findings suggestive of malignancy, hepatic, pulmonary, cardiac, or renal disease, or any other known causes of SIADH, we considered that hyponatremia was induced by meloxicam.

Hyponatremia (serum sodium concentration, <135 meq/L) is a potentially serious electrolyte disorder, and certain drugs (e.g., thiazide diuretics, antidepressants, clofibrate, antiepileptics) have been implicated as a common cause of hyponatremia in nonhospitalized individuals (2). NSAIDs are commonly prescribed by the physicians at the present time and can occasionally lead to hyponatremia by diminishing the normal inhibitory effect of prostaglandins on the activity of antidiuretic hormone (ADH) (2–5). NSAIDs appear to induce hyponatremia via facilitating the effects of ADH rather than via an increase in ADH secretion. NSAIDs may cause severe or mild hyponatremia presumably in relation to the duration of drug use in people who have risk factors (advanced age, heart failure, use of diuretics, and hypovolemia).

Animal studies suggest that prostaglandins have a little natriuretic effect in the euvolemic state, via reduced Na^+ reabsorption in the thick ascending limb and in the collecting tubules, but may play a role in the hypovolemic state in which prostaglandin synthesis increases. Nonsteroidal anti-inflammatory drugs have serious clinical consequences by inhibiting the synthesis of renal prostaglandins. Renal prostaglandins have both vascular and tubular actions (Table) (6–9).

NSAID-induced hyponatremia has been attributed to SIADH in studies, where the mechanism of hyponatremia associated with the use of NSAIDs was investigated (10–12). However, in some experimental studies, an increase in renal interstitial osmolality has also been suggested. In one study, it was shown that prostaglandin E2 (PGE_2) infusion caused a decrease in a corticomedullary gradient in rats, while indomethacin caused an increase (13). In other study, the administration of cyclooxygenase inhibitors in rats was shown to cause an increase in the protein levels of the NA-K-2Cl co-transporter that was partially reversed by misoprostol, a PGE_2-receptor agonist (14). These findings are suggestive of the mechanisms by which interstitial solute might be increased by NSAIDs.

Conclusions

Although hyponatremia induced by nonsteroidal anti-inflammatory drugs is rarely reported in the literature, it should be kept in mind in case of patients with hyponatremia, especially those who receive concomitant medications that may cause hyponatremia, or patients of advanced age, as was our patient.

Statement of Conflict of Interest

The authors state no conflict of interest.

Table. Renal Actions of the Prostaglandins and Possible Complications With Nonsteroidal Anti-Inflammatory Drugs

Effect of prostaglandins	Possible drug complications
Maintain renal blood flow and glomerular filtration rat by ameliorating angiotensin II and renal vasoconstriction	Acute renal failure in conditions associated with an increased release of renal vasoconstrictors
Antagonize systemic vasoconstriction	May raise blood pressure in treated hypertensive patients and can worsen cardiac output in heart failure due to increased afterload
Increase the secretion of rennin	Hyperkalemia due hyporeninemic hypoaldosteronism, primarily in patients with underlying renal insufficiency
Antagonize the action of antidiuretic hormone	Can potentiate a water-retaining effect of antidiuretic hormone, possibly promoting the development of hyponatremia
May increase sodium excretion in the states of effective volume depletion	May promote more intense sodium retention in edematous states and can impair response to diuretics

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