A Case of SIADH Induced by Mizoribin Administration

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Key Words

Syndrome of inappropriate secretion of antidiuretic hormone · Hyponatremia · Mizoribin · Drug · Disease-modifying antirheumatic drugs

Abstract

We describe a 74-year-old man with rheumatoid arthritis (RA) who developed syndrome of inappropriate secretion of antidiuretic hormone (SIADH) 1.5 months after commencement of mizoribin prescription when his arthritis was improved. He noticed nausea and headache and serum Na fell as low as 118 mEq/l. Normal urinary Na excretion without hypotension or hemoconcentration negated the possibility of dehydration resulting from urinary Na loss. Serum antidiuretic hormone (ADH) remained elevated at 0.59 pg/ml in spite of a significant reduction in serum osmolality to 254 mosm/kg. He had no organic disease likely to cause SIADH. Despite infusion of hypertonic saline, his serum Na was not restored to normal. Shortly after mizoribin withdrawal, his serum Na increased significantly from 128 to 139 mEq/l and plasma osmolality from 265 to 287 mosm/kg. ADH hypersecretion in relation to plasma osmolality was reversed by mizoribin withdrawal, suggesting that bredin-

in might adversely induce SIADH. Additional predisposing factors were the patient's age and difficulty in urination due to benign prostatic hypertrophy. In summary, we report herein the first case of SIADH believed to be an adverse effect of mizoribin, which may therefore needed to be added to the list of drugs which can induce SIADH.

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Introduction

A growing number of drugs cause syndrome of inappropriate secretion of antidiuretic hormone (SIADH) [1]. As the number of drugs used to treat rheumatoid arthritis (RA) has increased, these drugs, such as nonsteroidal anti-inflammatory drugs (NSAIDs), disease-modifying antirheumatic drugs (DMARDs) and immunosuppressive drugs such as cyclophosphamide and methotrexate, have been increasingly reported to cause SIADH [2,3]. Mizoribin has recently been introduced as an immunosuppressive drug for RA [4].

We reported herein the first case of SIADH as a putative adverse effect of mizoribin and the condition disappeared shortly after cessation thereof.

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Fig. 1. Influence of mizoribin administration on serum Na, serum ADH, and plasma osmolality. During mizoribin administration, serum ADH remained exceedingly high in relation to his serum Na and plasma osmolality. However, mizoribin withdrawal significantly increased serum Na and plasma osmolality without increasing serum ADH. On day 15 after mizoribin withdrawal, serum ADH showed normal relationship to plasma osmolality and serum Na. Day 0 is the day when mizoribin administration was withdrawn.

Fig. 2. Time-course changes in serum ADH and plasma osmolality during water challenge test. Water intake of 900 ml, i.e. 20 ml water/kg body weight, significantly suppressed serum ADH in a time-dependent manner until 2 h after water load, with the lowest level of 0.18 pg/ml at 2 h, and then increased it to 0.38 pg/ml at 3 h, indicating that serum ADH had returned to normal regulation by plasma osmolality.

Case Report

A 74-year-old man with RA was admitted to Osaka City University Hospital in 2000. He had past history of benign prostatic hyper trophy (BPH) when an increase of serum creatinine to 1.5 mg/dl had first been noticed although its etiology was unknown. In 1984, he initially noticed swelling of bilateral wrists, and was subsequently diagnosed with RA. He has taken various NSAIDs including sulindac, diclofenac sodium and DMARD including auranofin, but without development of SIADH. His arthritis worsened in May 2000. Although salazosulfapyridine (1,000 mg/day) was started in June 2000, followed by mizoribin at 75 mg daily 1 month later, his symptoms did not improve significantly. He was, therefore, admitted to our hospital on August 3 for further treatment. On the 12th hospital day, his symptoms had improved and CRP was decreased significantly from 4.4 to 2.2 mg/dl. We assumed that the improvement of his RA activity was accounted for mainly by the effect of mizoribin because the improvement occurred 1.5 months after commencement of mizoribin prescription. On the 15th hospital day, nausea and headache appeared suddenly. Biochemical data indicated severe hyponatremia as his serum Na had decreased to 118 mEq/l with significant reduction in plasma osmolality (254 mosm/kg) (table 1). Considering his plasma osmolality, his serum ADH level of 0.59 pg/ml was much higher than expected [5]. Na concentration in daily urine remained normal at 55 mEq/l with urine osmolality of 318 mosm/kg. Hyponatremia resulting from either hemoconcentration due to Na loss or pseudohyponatremia was negated. The presence of organic disease including heart, liver, adrenal and thyroid gland, which might cause water retention, was also excluded by the normal clinical data. SIADH could not be explained by lung or brain dysfunction because of no mass on computed tomography. As the

Table 1. Laboratory findings during hyponatremia

Blood urea nitrogen, mg/dl	20
Serum creatinine, mg/dl	1.47
Serum Na, mEq/l	118
Serum K, mEq/l	4.5
Serum Cl, mEq/l	83
Plasma osmolality, mosm/kg	254
Urine osmolality, mosm/kg	318
ADH, ng/ml	0.59
Fasting plasma glucose, mg/dl	101
Free T ₃ , pg/ml	1.7
Free T ₄ , ng/ml	1.3
TSH, μ IU/ml	1.043
Serum cortisol, μ g/dl	12.1
24-hour urine free cortisol, μ g/day	36
ACTH, pg/ml	40.3
Renin, ng/ml/h	0.24
Aldosterone, ng/ml	7.5

cause of drug-induced SIADH, since mizoribin was the most likely candidate as administration had started most recently, only about 1.5 months earlier, its administration was stopped on September 5 (fig. 1). Fifteen days later, serum Na was restored to the normal level of 139 mEq/l. The serum ADH level of 0.54 pg/ml restored a normal relationship with the plasma osmolality of 287 mosm/kg. In a water challenge test on September 20 (fig. 2), plasma osmolality decreased

significantly from 287 to 275 mosm/kg in 1 h and then hovered around 277 mosm/kg until 3 h after sufficient water intake of 900 ml. Serum ADH decreased in a time-dependent manner until 2 h after water load with the lowest level of 0.18 pg/ml at 2 h, and then increased to 0.38 pg/ml at 3 h, confirming that serum ADH had returned to normal regulation by plasma osmolality.

Discussion

We report herein the first case of SIADH believed to be an adverse effect of mizoribin. This patient had no endocrine disease such as adrenal insufficiency or hypothyroidism to induce hyponatremia [6]. Furthermore, he had no renal, hepatic or cardiac disease to induce water retention. His urinary Na excretion and urine osmolality remained normal in spite of severe hyponatremia. Plasma contraction was also unlikely because of the absence of hypotension or increased serum creatinine or plasma hemoglobin. Additional risk factors for SIADH were the patient's age of 74 years and decreased urine production due to the difficulty in urination caused by BPH. The pos-

sibility of tumor disease, which produces ADH autonomously, was also excluded. Evidence supportive of mizoribin-induced SIADH was the restoration of a normal relationship between serum ADH and plasma osmolality after mizoribin withdrawal, which was confirmed by the water challenge test (fig. 2). Of interest, it took as long as almost 1.5 months for mizoribin to cause SIADH simultaneously with efficacy against RA. Drugs used for the treatment of RA induce SIADH chemically within as little as 10 days after initial administration [1–3]. DMARDs often cause major adverse effects immunologically when the effect of the drug becomes evident. Although these observations may suggest that mizoribin may induce SIADH via the immune system, it is still possible that mizoribin causes ADH oversecretion directly, since serum Na restored to normal shortly after mizoribin withdrawal.

In summary, we described the first known case of SIADH believed to be an adverse effect of mizoribin in RA patients. Mizoribin may thus be necessary to be added to the list of drugs that can induce SIADH.

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