Severe Hyponatremia and Hyperkalemia Induced by Trimethoprim-Sulfamethoxazole in Patients with Pneumocystis carinii Pneumonia

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An antimicrobial agent trimethoprim-sulfamethoxazole (Tmp-Smx) does not usually cause electrolyte disturbances at regular doses, and few cases of Tmp-Smx-induced electrolyte imbalance have been reported in the English-language literature to date. Recently, however, we treated two patients with Pneumocystis carinii pneumonia who developed severe hyponatremia and hyperkalemia on administration of high-dose Tmp-Smx. These electrolyte disturbances were attributable to the direct effect of Tmp-Smx on the renal distal tubules, were reversible, and corrected by infusion of a sodium-enriched and potassium-free liquid. Therefore, it is suggested that even after electrolyte disturbances have occurred, high-dose Tmp-Smx therapy may be continued for severe infectious diseases under appropriate electrolyte correction.

Key words: metabolic acidosis, AIDS

Introduction

Trimethoprim-sulfamethoxazole (Tmp-Smx) is an antimicrobial agent which is effective for Pneumocystis carinii infection. This drug is excreted from the kidney and is known to have side effects such as acute tubular necrosis and interstitial nephritis (1–3). Tmp-Smx has been reported to cause renal salt wasting and metabolic acidosis (4), but appears to have no remarkable effects on serum electrolyte levels as long as regular-dose Tmp-Smx is administered (5). However, recent reports demonstrate that hyperkalemia occurred in patients with AIDS and Pneumocystis carinii pneumonia who were treated with high-dose Tmp-Smx (6–8). In most of those cases, a causal relation between the Tmp-Smx treatment and hyperkalemia is suggested but not proven because of the simultaneous presence of complications such as renal failure, adrenal insufficiency, and hypoaldosteronism (9–12). Recently, we experienced two cases with severe hypo-natremia and hyperkalemia associated with high-dose Tmp-Smx therapy. In contrast to the patients with AIDS who have been reported, our cases are free from complications which may cause electrolyte disturbances. Therefore, Tmp-Smx is suggested to act directly on the distal nephrons, causing a decrease in the renal sodium reabsorption and the renal potassium excretion.

Case Reports

Case 1

A 64-year-old man was admitted because of night sweat and fever. Physical examination revealed lymph node enlargement. A chest X-ray film showed bilateral hilar lymphadenopathy with no other abnormality in the bilateral lungs. The biochemical data were as follows: total protein 7.4 g/dl, albumin 3.5 g/dl, sodium (Na) 139 mmol/l, potassium (K) 4.5 mmol/l, chloride (Cl) 102 mmol/l, blood urea nitrogen (BUN) 12.4 mg/dl, creatinine 1.0 mg/dl, uric acid 6.4 mg/dl, lactate dehydrogenase (LDH) 321 IU/l (normal, 83–166 IU/l), alkaline phosphatase (ALP) 428 IU/l (normal, 66–220 IU/l), and C-reactive protein (CRP) 7.3 mg/dl. White blood cell (WBC) count, hemoglobin (Hb), and platelet count were 5.4x10^9/l, 11.2 g/dl, and 213x10^9/l, respectively. He was diagnosed as Hodgkin's disease (mixed cellularity) on lymph node biopsy. After 5 courses of VEPA regimen (vincristine 1 mg/day, endoxan 30 mg/day, prednisolone 40 mg/day, and adriamycin 40 mg/day), both clinical and laboratory findings improved (LDH 171 IU/l, ALP 196 IU/l, and CRP 0.3 mg/dl).

However, he developed fever and hypoxemia (PO2 65.6 mmHg on room air), and chest X-ray films and computed tomography (CT) showed diffuse shadows in the bilateral

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Antibiotic-Induced Electrolyte Imbalance

Case 1

Lungs. Pneumocystis carinii pneumonia was suspected and Tmp-Smx (12 g per day) was given. Thereafter, the serum levels of sodium and potassium began to change (Figs. 1, 2). Though oral intake plus intravenous infusion of sodium and potassium per day were around 300 mmol and 50 mmol respectively, the potassium concentration increased to 6.6 mmol/l after 3 days of administration and the serum sodium concentration decreased to 109 mmol/l after 4 days. In association with the development of hyponatremia, his consciousness level decreased. He had no abnormality in ECG. Serum creatinine remained between 0.7 and 1.0 mg/dl, while BUN was between 9.0 and 12.0 mg/dl. Creatinine clearance was 94 ml/min and fractional excretion of sodium (FENa) was 2.6%. These indicated that the electrolyte disturbances were not due to a reduced renal function. In addition, the decrease in serum sodium was associated with increased urinary sodium excretion, while the increase in serum potassium was associated with inhibited urinary potassium excretion (Figs. 1, 2). From this, it was supposed that the electrolyte abnormalities might be corrected by changing the amount of electrolytes in the infusion fluid. Therefore, from the 6th day of the Tmp-Smx treatment, a fluid with high sodium (380 mmol per day) and no potassium was infused. The severe hyponatremia and hyperkalemia were corrected promptly and his consciousness was recovered. At this time, creatinine clearance was 90 ml/min and FENa was 3.5%. After 11 days of the Tmp-Smx treatment, Tmp-Smx was discontinued because the chest X-ray and CT findings of the pneumonia improved and pancytopenia developed (WBC count 2.8×10^9/l, Hb 5.8 g/dl, and platelet count 76×10^9/l). Then, the sodium excretion into the urine decreased and the potassium excretion into the urine continued, and both serum sodium and potassium levels returned to the normal range. The infusion was changed to the previous one, containing 150 mmol of sodium and 50 mmol of potassium per day (Figs. 1, 2). The electrolyte disturbances disappeared and the pancytopenia induced by Tmp-Smx resolved.

On the other hand, the Hodgkin’s disease deteriorated 3 months later. He had high-grade fever and laboratory study revealed the following values: LDH 307 IU/l, ALP 2,223 IU/l, and CRP 10.6 mg/dl. From these data, an infiltration of Hodgkin cells into the liver was suspected and he was treated with ABVD regimen (adriamycin 30 mg/day, bleomycin 10 mg/day, vinblastine 8 mg/day, and dacarbazine 500 mg/day). Regular-dose Tmp-Smx (2 g per day) was given prophylactically against expected Pneumocystis carinii pneumonia following drug-induced agranulocytosis. During the course of this regular-dose Tmp-Smx treatment, neither hyponatremia nor hyperkalemia has ever been recognized.

Case 2

A 59-year-old man was admitted for chemotherapy of acute myeloblastic leukemia. He was afebrile, and WBC count, Hb, and platelet count were 17.4×10^9/l, 6.9 g/dl, and 72×10^9/l, respectively. Differential count of WBC was as follows: blastocytes 60%, myelocytes 0%, metamyelocytes 0%,

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neutrophils 26%, eosinophils 1%, monocytes 3%, basophils 0%, and lymphocytes 10%. The biochemical data were: total protein 6.7 g/dl, albumin 3.6 g/dl, Na 135 mmol/l, K 5.2 mmol/l, Cl 105 mmol/l, BUN 52.9 mg/dl, creatinine 1.7 mg/dl, LDH 356 IU/l, ALP 271 IU/l, and CRP 6.5 mg/dl. Chemotherapy with hydroxyurea and Ara-C was started, but the growth of leukemia cells was uncontrollable.

At 6 months after admission, his WBC count, Hb, and platelet count were 71.9 x 10^9/l, 6.9 g/dl, and 1.6 x 10^9/l, respectively. Serum creatinine was 0.9 mg/dl and BUN remained between 12 and 26 mg/dl. These data indicated that renal function had improved. At that time, however, *Pneumocystis carinii* pneumonia was suspected on chest X-ray films, and Tmp-Smx was given at a dose of 12 g a day. Biochemical data at the beginning of the Tmp-Smx treatment were: Na 141 mmol/l, K 2.7 mmol/l, Cl 105 mmol/l, BUN 14.9 mg/dl, creatinine 0.9 mg/dl, and FENa 0.3%. Blood gas analysis was as follows: pH 7.489, PCO2 35.9 mmHg, PO2 90.6 mmHg, and bicarbonate 27.3 mmol/l on oxygen at 3 l/min. On the 6th day of the Tmp-Smx administration, Na, K, Cl, BUN, and creatinine were 126 mmol/l, 5.2 mmol/l, 104 mmol/l, 29.1 mg/dl, and 1.1 mg/dl, respectively (Figs. 3, 4). In association with this electrolyte disturbance, marked metabolic acidosis developed (pH 7.293, PCO2 27 mmHg, PO2 151 mmHg, and bicarbonate 13 mmol/l on oxygen at 3 l/min), but his consciousness level was not altered. Urine study showed that the sodium excretion into the urine increased and FENa increased from 0.3% to 3.3% in spite of the low serum sodium level, while the potassium excretion into the urine did not increase remarkably even with the elevated serum potassium level (Figs. 3, 4). Creatinine clearance was between 50 and 65 ml/min. From these results, it is supposed that the electrolyte abnormalities might be corrected by changing the amount of electrolytes in the infusion fluid. On the 7th day, therefore, the sodium infusion was increased to 300 mmol per day and potassium-free fluid was used, which rapidly corrected the abnormal serum electrolyte levels (Figs. 3, 4). On the 10th day, Tmp-Smx was replaced by pentamidine since the pneumonia did not improve. Thereafter, concentrations of serum sodium and potassium, FENa, and creatinine clearance were settled within normal ranges. BUN and creatinine returned to the previous levels and the metabolic acidosis disappeared.

**Discussion**

Electrolyte disturbances are considered to be very rare adverse effects of Tmp-Smx when it is given at regular doses (6–8). At high doses, however, Tmp-Smx is expected to induce hyponatremia and hyperkalemia, since this drug has been reported to cause renal salt wasting (4). In the present two cases, high-dose Tmp-Smx (12 g per day) decreased serum sodium and increased serum potassium. In spite of the low serum sodium and high serum potassium levels, the sodium excretion into the urine increased while the potassium excretion into the urine did not increase significantly. These data suggest that
Tmp-Smx at high doses inhibits sodium reabsorption and potassium excretion in the renal distal tubules.

Trimethoprim (Tmp) is a heterocyclic weak base structurally related to amiloride which is a potassium-sparing diuretic agent. Tmp acts the same way as amiloride: it blocks reabsorption of sodium in the distal tubules, decreasing the lumen-negative transepithelial voltage. This secondarily decreases potassium secretion and induces hyperkalemia (5, 7, 8). Recent animal experiments also suggest that Tmp reversibly inhibits renal potassium secretion in a dose-dependent manner (6–8). From these findings, it can be speculated that the electrolyte disturbances seen in our present two cases are due to a direct action of Tmp-Smx on the renal distal tubules.

According to the recent reports on AIDS patients with Pneumocystis carinii pneumonia, hyperkalemia is recognized in 44 to 70% of patients who are given Tmp-Smx at high doses (6–8, 13–16). This hyperkalemia is also supposed to be due to high-dose Tmp-Smx therapy which causes reduced sodium reabsorption and potassium excretion in the distal tubules. However, many of these patients had severe complications such as renal failure and adrenal insufficiency which have profound effects on serum electrolytes. Therefore, it was difficult to interpret the action of Tmp-Smx accurately. In contrast, our present two cases have no severe complications which could cause severe electrolyte disturbances. The adrenal functions of these patients appeared to be preserved, since no suggestive symptoms and signs of adrenal insufficiency were appreciated and CT findings of adrenal glands were normal. This provides further support for the speculation that Tmp-Smx at high doses acts directly on the renal distal tubules and thereby inhibits sodium reabsorption and potassium excretion. On the other hand, reuptake of sodium is supposed to be moderately inhibited by regular-dose Tmp-Smx (6–8). However, no significant changes were observed in serum sodium and potassium levels of those AIDS patients and our case one when treated with regular-dose Tmp-Smx. This suggests the possible existence of some unknown mechanisms which can compensate mild hyponatremia and hyperkalemia.

In our present two cases, hyperkalemia and hyponatremia developed rapidly after the administration of high-dose Tmp-Smx and resolved spontaneously on its discontinuation. This points to a possibility that Tmp-Smx alters sodium reabsorption and potassium excretion without causing any irreversible organic damage to the distal tubules. Moreover, Tmp-Smx-induced electrolyte disturbances can be corrected by sodium infusion and potassium deprivation. Therefore, when absolutely indicated for severe infections, high-dose Tmp-Smx therapy can be continued as long as severe adverse effects other than electrolyte disturbances are not observed. To enable continuous use of high-dose Tmp-Smx on patients showing abnormal electrolyte concentrations, frequent measurement of both serum and urinary electrolytes and careful correction of serum electrolyte levels with infusion are necessary.

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References