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Elevated serum lithium concentration due to the voluntary refusal to eat and drink

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We report a case of increased serum lithium concentration due to the decreased sodium chloride intake, which was caused by the patient's refusal to eat and drink. A 76-year-old male inpatient received lithium carbonate orally at 200-600 mg/day for the treatment of the manic phase of bipolar disorder. His serum lithium concentration reached 0.61-0.85 mEq/L. Because the patient had difficulty eating due to pneumonia, he received parenteral nutrition. Because of the patient's voluntary refusal of parenteral nutrition, enteral nutrition by oral route was started. Upon receiving enteral nutrition, the patient voluntarily refused to eat, significantly decreasing his nutrition intake and lowering his sodium chloride intake by 6.6-11.5 g/day than that by parenteral nutrition. As a result, the patient's dietary salt intake was decreased, which led to an increase in serum lithium concentration. In addition, the patient's voluntary refusal to drink water markedly reduced his water intake, leading to dehydration and increased serum lithium concentration. At 17 days after the start of enteral nutrition by oral route, the patient's serum lithium concentration increased to 2.59 mEq/L and his serum sodium concentration was 147 mEq/L, but no adverse event occurred. Enteral nutrition was immediately discontinued and parenteral nutrition was started. Because the patient received a sufficient amount of water and sodium chloride intake, his serum lithium concentration rapidly decreased to 1.56 mEq/L. Enteral nutrition by oral route was subsequently started; however, because of the decrease in sodium chloride intake due to the refusal of food, the decrease in the serum lithium concentration was gradual, with the concentration decreased to 0.20 mEq/L.

Key Words: Lithium; drug-level monitoring; sodium chloride intake; parenteral nutrition; enteral nutrition

Introduction

Lithium carbonate is a widely used drug for the treatment of the manic phase of bipolar disorder (manic-depressive illness). Patients receiving this drug are required to be monitored for serum lithium concentration to prevent lithium overdose and subsequent toxicity. The use of this drug is also contraindicated for patients prone to lithium accumulation in the body [1)].

Enteral nutrition is a feeding method that is more physiological than parenteral nutrition. Therefore, to prevent atrophy of the intestinal mucosa, enteral nutrition supply is preferred for patients with a functioning intestine [2)]. It has been reported that lithium carbonate administration to patients receiving enteral nutrition is associated with an increase in serum lithium concentration and a decrease in total sodium chloride intake [3)]. In addition, it is possible to prevent increased serum lithium concentration in these patients by increasing the sodium chloride intake with oral administration of sodium chloride [4)].

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Here, we report a case of increased serum lithium concentration due to the decreased sodium chloride intake, which was caused by the patient's refusal to eat and drink.

Case report

A 76-year-old male inpatient received lithium carbonate orally at 200-600 mg/day for the treatment of the manic phase of bipolar disorder (manic-depressive illness). His serum lithium concentration reached 0.61-0.85 mEq/L. Because the patient had difficulty eating due to pneumonia, he received parenteral nutrition (water intake: 1,100-1,700 mL/day; energy intake: 86-186 kcal/day; sodium chloride intake: 5.9-11.7 g/day) from day 1 to day 20. Because of the patient's voluntary refusal of parenteral nutrition, his energy intake was decreased. The patient's serum sodium concentration remained within the reference range, at 141-143 mEq/L (Fig.1).

In the present case, 400 mg/day oral lithium carbonate had been administered for approximately the past 7 years and 6 months (day -2,744) and the dose was increased to 600 mg from day -18 to day 8 (day 9 was 200 mg/day) because of delusions and damage to property. However, lithium carbonate administration was discontinued from day 10 to day 16, owing to a 37.9 ° C fever (axillary temperature) and sweating, which were caused by a cold. On day 17, axillary temperature had dropped to 36.3 ° C, so the oral administration of lithium carbonate was restarted at 400 mg/day.

Because of the patient's voluntary refusal of parenteral nutrition, enteral nutrition by oral route was started at day 21, 17 days before the discontinuation of oral lithium carbonate administration. Upon receiving enteral nutrition, the patient voluntarily refused to eat, significantly decreasing his nutrition intake (energy intake: 210-1,050 kcal/day; sodium chloride intake: 0.2-1.2 g/day) and lowering his sodium chloride intake by 6.6-11.5 g/day than that by parenteral nutrition. As a result, the patient's dietary salt intake was decreased, which led to an increase in serum lithium concentration. In addition, the patient's voluntary refusal to drink water markedly reduced his water intake (150-200 mL/day), leading to dehydration and increased serum lithium concentration.

At day 38 (17 days after the start of enteral nutrition), the patient's serum lithium concentration increased to 2.59 mEq/L and his serum sodium concentration was 147 mEq/L, but no adverse event occurred. The administration of lithium carbonate was discontinued because of the increased serum lithium concentration. At day 38, enteral nutrition by oral route was immediately discontinued and parenteral nutrition was started (water intake: 1,000-1,700 mL/day; energy intake: 86-510 kcal/day; sodium chloride intake: 6.0-8.7 g/day). The patient also had pyrexia due to infection and was thus concomitantly treated with piperacillin-tazobactam (2 g/day). Three days after the start of parenteral nutrition (at day 41), because the patient received a sufficient amount of water and sodium chloride intake, his serum lithium concentration rapidly decreased to 1.56 mEq/L. Enteral nutrition by oral route was subsequently started; however, because of the decrease in sodium chloride intake due to the refusal of food, the decrease in the serum lithium concentration was gradual, with the concentration decreased to 0.20 mEq/L in 17 days. Additionally, the serum sodium concentration during this period was 143-148 mEq/L (Fig.1).

Moreover, during this period, the patient showed high serum concentrations of electrolytes (potassium: 2.8 to 4.6 mEq/L; chloride: 103-114 mEq/L; sodium: 141-148 mEq/L) and the levels of renal function markers also deviated from the reference ranges (serum creatinine: 0.73-1.20 mg/dL; estimated glomerular filtration rate: 45.9-79.0 mL/min/1.73 m^2; blood urea nitrogen, 9.2-55.5 mg/dL). During the 6-month period of this study, the patient's body weight and body mass index decreased from 74.4 kg to 54.7 kg and from 26.7 to 19.6, respectively.

Discussion

In the present case, because the elevated serum lithium concentration was a result of the patient's refusal to eat and drink, enteral nutrition was discontinued and parenteral nutrition was resumed. After resuming parenteral nutrition, the patient's sodium chloride intake was recovered,

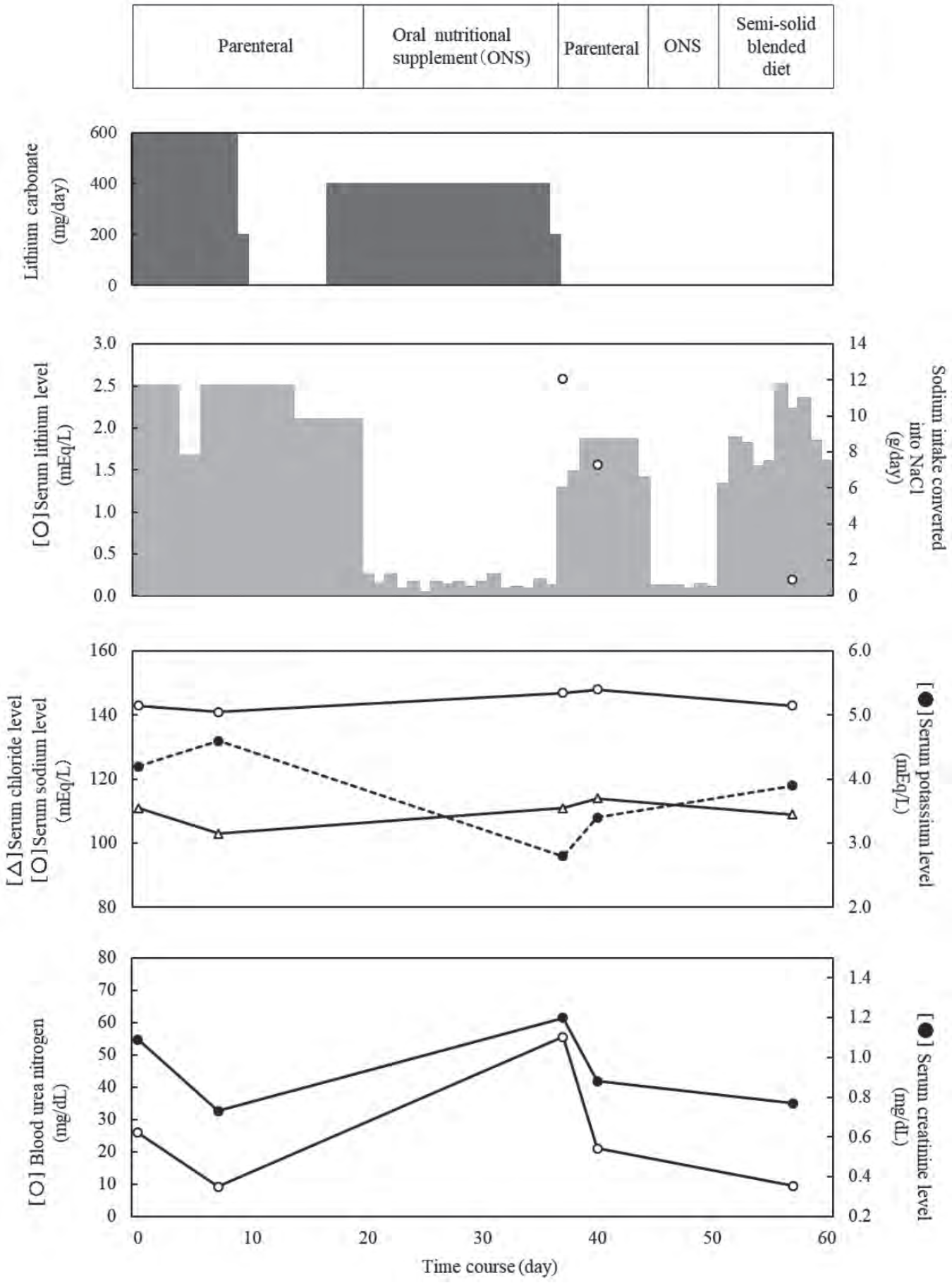

Fig. 1 Serum lithium concentration, electrolyte concentrations, renal function marker levels, and nutrition intake of the patient.

resulting in a prompt decrease in the serum lithium concentration. However, the patient voluntarily refused parenteral nutrition and subsequently resumed enteral nutrition. Again, the patient's refusal to eat caused a decrease in sodium chloride intake, leading to the persistence of high serum lithium concentration.

The Japanese dietary reference [6] specifies that in men aged 70 years or older, the average required sodium intake is 1.5 g/day from sodium chloride and less than 7.0 g/day from sodium chloride equivalents. On the other hand, the sodium intake of this patient was 0.4-1.2 g/day, which is below the average requirement. Although the sodium intake was decreased due to the refusal to eat and drink, the serum sodium concentration did not markedly change and remained within the reference range. However, a study was conducted to investigate the association between the amount of urinary sodium excretion and lithium clearance following the gradual reduction of the normal dietary intake of sodium chloride [7]. The results showed that along with a decrease in urinary sodium excretion, lithium clearance decreased. Similarly, in this patient, the decrease in sodium intake, which was caused by his refusal to eat and drink, led to the increased reabsorption of sodium ion in the renal tubule, relatively increased reabsorption of lithium ion, and decreased lithium clearance, which resulted in the increased serum lithium concentration.

Another cause of the increased serum lithium concentration was renal impairment due to dehydration, which resulted from the voluntary refusal to drink water. Although the urine volume was not measured, the voiding frequency was low at 1-4 times/day (2.2 times on average) and the excretion of concentrated urine was noted. Because the patient's body weight remained at approximately 55 kg, the increased serum lithium concentration was considered to be caused by the deterioration of renal function due to dehydration.

Lithium carbonate requires the most careful dosing for patients with deterioration of renal function. Dose reduction is unnecessary when the patient shows creatinine clearance (CCr) of over 50 mL/min. However, it is necessary to reduce the dose by 30-50 % when the patient's CCr is 10-50 mL/min, and by 50-75 % when the CCr is below 10 mL/min [5]. In the current study, as calculated using the Cockcroft-Gault (CG) formula, the patient's CCr was 53.2-72.8 mL/min, showing a mild to moderate renal function deterioration. Thus, the dose of lithium carbonate need not be reduced. However, when the patient's serum lithium concentration was elevated, his CCr was 40.5 mL/min, showing the lowest level of renal function.

The patient was a thin, aged man with a serum creatinine level less than 0.6 mg/dL and declined muscle mass. This serum creatinine value was used to calculate the CCr using the CG formula, which resulted in a CCr value of 88.6 mL/min. In consideration of the patient's highly impaired renal function, the serum lithium concentration was measured and the dose of lithium carbonate was carefully selected. Furthermore, the estimated glomerular filtration rate without correction for body surface area was 51.1-76.3 mL/min, showing a mild to moderate decline in renal function. During the period of increased serum lithium concentration, the estimated glomerular filtration rate was 42.6 mL/min, representing the lowest level of renal function. On the basis of the CCr and glomerular filtration rate, the decreased lithium clearance due to the impaired renal function was considered as one of the causes of the increased serum lithium concentration.

Additionally, we assessed the association between a concomitant drug and the increased concentration of serum lithium in this patient. Valsartan, an angiotensin II-receptor antagonist, was administered at 40 mg/day and did not affect serum lithium concentration. Oral administration of valsartan (40 mg/day) was started on day -268 and continuously administered since then, with no discontinuations. Previous reports have shown that the co-administration of angiotensin II receptor antagonists and lithium carbonate increased serum lithium concentration from 36% to 75% [8), 9)]. Therefore, it is believed that serum lithium concentration should be measured approximately once per week until 1 month after the co-administration was started. Seven days before valsartan was administered in the present case, the serum lithium concentration was 0.61 mEq/L and

the serum sodium concentration was 135 mEq/L. The serum lithium concentration 7 days after valsartan administration was started was 0.65 mEq/L; 1 month later, it was 0.63 mEq/L. It increased from 3% to 7%, but large variations were not observed. The serum sodium concentration was 137 mEq/L 1 month after valsartan administration. Thus, in this patient, the increased serum lithium concentration was not attributed to the concomitant drug. Symptoms of lithium toxicity have also been shown to occur from between 3 and 5 weeks after starting co-administration of angiotensin II receptor antagonists and lithium carbonate [8]. In the present case, lithium carbonate and valsartan were co-administered continuously for 298 days; and despite careful monitoring of the status of the patient, lithium toxicity symptoms did not occur.

As shown above, in this patient, the lithium clearance was reduced due to the moderately impaired renal function. The lithium clearance reduction was also caused by renal impairment due to dehydration and by the decreased sodium chloride intake. All these were considered results of the increased serum lithium concentration. It was shown that lithium-ion has a similar behavior to and is largely affected by sodium ion [10), 11)]. Therefore, it is important to control sodium ion concentration in the body by adjusting the salt content in the diet or in the infusion. Particularly in the cases where the dose of lithium carbonate should be reduced due to renal function deterioration, sodium intake needs to be managed more carefully.

In cases where serum lithium concentration elevates due to the refusal to eat and drink, sufficient sodium chloride intake should be maintained via parenteral nutrition; otherwise, the patient's serum lithium concentration will remain high. In addition, parenteral nutrition should be continued until a sufficiently low serum lithium concentration has been confirmed, at which point the patient should switch to enteral nutrition. After the switch to enteral nutrition, there is a possibility of another increase in serum lithium concentration due to the patient's refusal to eat and drink. Therefore, the patient's blood should be frequently measured for lithium concentration.

Ethical considerations

We obtained approval for the planning of this case study from the clinical research ethics committee of Hospital Bando.

Conflict of interest

The authors declare no conflict interest.

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