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A case of linezolid-induced SIADH in elderly and a review of the literature

Q.-W. DONG[1], L. TANG[2], D.-D. GE[1], T.-Y. ZHOU[2], Y.-C. ZHAO[2], C.-H. MA[2], P. SUN[2]

[1]Department of Orthopedics, [2]Department of Endocrinology, the First Affiliated Hospital of Guangdong Pharmaceutical University, Guangzhou, China

Qunwei Dong, Lin Tang and Dongdong Ge contributed equally to this work

Abstract. – INTRODUCTION: Linezolid is a synthetic oxazolidinone antimicrobial drug with a broad spectrum and a unique mechanism of inhibiting resistant pathogenic strains, and it was approved by the Food and Drug Administration (FDA) in April 2000. Several different systemic side effects were reported after the use of this medication. In this article, we report a case in which a syndrome of inappropriate antidiuretic hormone (SIADH) was developed after linezolid treatment was started.

CASE PRESENTATION: We present the case of a 79-year-old woman who developed severe hyponatremia during linezolid treatment (0.6 g i.v. q12 h) after undergoing hemiarthroplasty for left femoral neck fracture. The patient's baseline serum sodium upon admission (138 mmol/L) decreased to 118 mmol/L, urine sodium was 102 mmol/L, plasma osmolality was 248 mOsm/kg and urine osmolarity was 310 mOsm/kg at day 4, thus a diagnosis of SIADH was made. The patient was not taking any other medication known to cause SIADH, and she did not present a comorbidity that could explain her condition. Her serum sodium increased to 135 and 137 mmol/L, respectively, 11 and 12 days after cessation of linezolid, strongly suggesting that SIADH was the cause in this case.

CONCLUSIONS: This is the fourth case of linezolid-induced SIADH. A thorough workup was essential for the diagnosis to correctly differentiate between SIADH and other causes of hyponatremia, which helped us properly conducting follow-up treatments. SIADH is a rare but serious side effect of linezolid, and practicing physicians should be aware of this complication. It is necessary to periodically monitor the serum sodium.

Key Words:
Case report, SIADH, Hyponatremia, Linezolid.

Introduction

Hyponatremia is a common electrolyte disturbance in hospitalized patients. Approximately half of elderly patients with hyponatremia present features that are typical of the syndrome of inappropriate antidiuretic hormone secretion (SIADH), and these features may be caused by physiological changes, disease processes or drugs[1]. Oxazolidinones comprise a new class of synthetic antimicrobial drugs, followed by sulfanilamide and fluoroquinolones. Linezolid was the first pharmacologically active compound developed and the first synthetic oxazolidinone approved for clinical use[2]; the drug has been described to cause mild hyponatremia in up to 18% of patients, while severe hyponatremia (≤128 mEq/L) is extremely rare (1.6% of patients); however, the mechanism is not clear, and is generally not considered to be associated with SIADH[3,4]. Three cases have been reported[5-7] so far by Baik et al[5], who developed SIADH during a treatment with linezolid and buspirone; Sumeet et al[6] and Ioannou et al[7], who presented cases of linezolidinduced SIADH.

Case Presentation

A 79-year-old woman developed severe hyponatremia during treatment with linezolid due to an infection, which occurred after hemiarthroplasty was performed for a left femoral neck fracture. Before admission, the patient was in her usual state of health. She had a history of asymptomatic lacunar cerebral infarction for decades and took simvastatin (20 mg once daily), clopidogrel (75 mg once daily) and calcium (occasionally). The patient had no known drug or food allergies at the time.

Corresponding Authors: Ping Sun, MD; e-mail: sing_ping928@gdpu.edu.cn
Chonghong Ma, MD; e-mail: mch2203@163.com

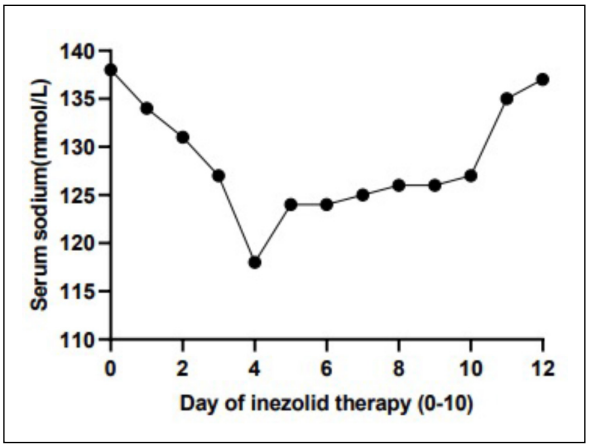

Figure 1. Serum sodium values during linezolid therapy. The horizontal axis shows the day of linezolid therapy. The vertical axis shows the serum sodium in mmol/L. Linezolid was stopped at day 10.

Upon physical examination, the patient exhibited stable vital signs and normal cognitive function. Other findings were unremarkable except for the fracture of her left femoral neck. Initial laboratory findings revealed that her serum sodium was 138 mmol/L, serum potassium was 3.5 mmol/L, serum chloride was 100 mmol/L, blood urea nitrogen was 5.31 mmol/L, serum creatinine was 61 μmol/L, serum uric acid was 211 μmol/L, and serum procalcitonin was 0.104 ng/mL (normal range 0-0.05 ng/mL). Her complete blood count was normal. After hemiarthroplasty was performed for her left femoral neck fracture, the patient developed a fever (39.6°C) the next day, and linezolid (0.6 g i.v. twice daily) was admitted due to empirical anti-infection treatments. A chest CT showed that slight pneumonia had developed and did not show any evidence for a pulmonary oedema or mass that was suggestive of malignancy; a brain CT was consistent with a previous lacunar cerebral infarction, but was otherwise unremarkable; blood cultures and urine cultures were sterile, and an abdominal ultrasound and heart ultrasound did not show any signs of infection.

On day 2 of linezolid administration, serum sodium was 131 mmol/L and a middle-grade fever of 38.8°C was present, serum sodium was 127 mmol/L at day 3 with the fever of 38.1°C, and serum sodium was 118 mmol/L at day 4 with low-grade fever of 37.5°C. The patient seemed somnolent. The plasma osmolality was 248 mOsm/kg, urine osmolarity was 310 mOsm/kg, and urine sodium was 102 mmol/L. The blood cortisol at 8 AM was 513.09 nmol/L (normal range 101.2-535.7 nmol/L), 4 PM was 326.9 nmol/L (normal range 101.2-535.7 nmol/L), 00 AM was 418.3 nmol/L (normal range 101.2- 535.7 nmol/L), the plasma adrenocorticotropic hormone concentration (ACTH) was 4.6 pmol/L (normal range 0-10.212 pmol/L), serum urea nitrogen was 6.64 mmol/L, and serum creatinine was 38 μmol/L. TSH was 0.94 μIU/ml (normal range 0.35-4.94 μIU/ml), and tumor markers (CEA, CA199, CA125, AFP, CA153, CA724) were normal. Therefore, fluid restriction was performed, and hypertonic saline was administered, but the hyponatremia did not resolve. We searched the PubMed database, and a review of the current literature indicated that simvastatin and clopidogrel have not been reported to be associated with SIADH, while linezolid has been reported[4-6], so it was stopped immediately. The following day, serum sodium increased rapidly to 135 mmol/L, and on the next day, the serum sodium increased to a normal sodium level of 137 mmol/L. The patient was not prescribed any medication during the hospital stay that were known to cause SIADH, and further work-up did not reveal other potential causes of SIADH. According to the adverse drug reaction probability scale by Naranjo et al[8], this case was assigned a score of 6. Based on the laboratory and clinical findings, linezolid-induced SIADH and the lack of hyponatremia recurrence were consistent after stopping linezolid in this case. The patients' serum sodium levels are shown in Figure 1.

Discussion

SIADH is a well-known cause of hyponatremia, and it can occur secondary to medications, such as amiodarone[9], pulmonary disease, malignancy (such as small cell lung cancer), central nervous system disorders, and COVID-19[10]. In this case, SIADH developed rapidly after initiating linezolid, and the serum sodium started to increase immediately after linezolid was discontinued. The drugs provided to the patient included simvastatin, clopidogrel and calcium (occasionally), which were not reported to induce SIADH. At the same time, there was no evidence for adrenal insufficiency or hypothyroidism and malignant disease, or CNS disorder based on thorough work-ups. Notably, SIADH occurred with linezolid and resolved after linezolid was stopped, which firmly suggests that linezolid was the aetiologic agent for SIADH in this case.

The first case report of hyponatremia during linezolid treatment was presented by Suzuki et al[3]

in 2008, it occurred in Japan, where a 75-year-old man with acute myeloid leukemia developed severe hyponatremia (serum sodium was 119 meq/L) after linezolid administration. Because the man was dehydrated, hyponatremia was attributed to renal salt-wasting syndrome rather than SIADH in that case. Baik et al[5] reported a case of SIADH that was induced by linezolid. That case involved an 81-year-old Korean woman who had a history of myringectomy due to otitis media of the left ear 10 years previously; and a stroke with left-sided hemiplegia 4 years previously. Her medications included buspirone hydrochloride, memantine hydrochloride, and cilostazol. Twenty-two days after starting the linezolid treatment, her serum sodium decreased to 118 meq/L, urine sodium was 1183 meq/L, serum and urine osmolarity values were 250 and 357 mOsm/kg, respectively, so SIADH was diagnosed. After linezolid was discontinued, the serum sodium increased to 135 meq/L the next day and remained stable until she was discharged from the hospital. Sumeet et al[6] presented a case of an 82-years-old man with no chronic comorbidities. Ten days after start of linezolid, his serum sodium was 119 mEq/L, serum and urine osmolality were 254 and 433 mOsmol/kg, respectively, so a diagnosis of drug-induced SIADH was made. Unfortunately, the patient eventually passed away due to an acute lung injury that was secondary to aspiration. Ioannou et al[7] reported an 89-year-old woman who developed severe hyponatremia during treatment with linezolid, hyponatremia occurred after linezolid was started and resolved after it was stopped, suggesting that linezolid was the aetiologic agent for SIADH in this patient. To the best of our knowledge, the exact mechanism of SIADH induction with linezolid has not been defined. First, its mechanistic effects on the central nervous system have yet to be explained and maybe directly stimulate the release of AVP in the CNS due to adverse reactions associated with the CNS, such as headaches, insomnia, dizziness, and vertigo[5]. Second, it is unclear whether there is any genetic linkage, such as the optrA8 gene[11,12], that may explain the susceptibility to SIADH induction following the administration of linezolid.

Conclusions

In our case, the patient developed severe hyponatremia and met all the diagnostic criteria for SIADH. Further investigation of alternative causes of SIADH failed to find any related diseases and medications. Although this complication is uncommon, it can be quite severe. We strongly suggest that the serum sodium levels of patients who are treated with linezolid should be continuously monitored. In summary, physicians should be aware of this rare side effect of linezolid, which can induce potentially life-threatening hyponatremia.

Conflict of Interest

The authors declare no conflicts of interest.

Informed Consent

Obtained.

Ethics Approval

Obtained.

ORCID ID

Ping Sun: 0000-0002-7776-2930

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