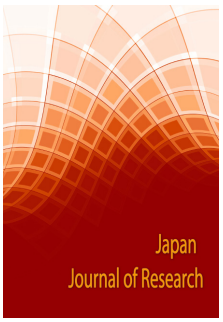
Japan Journal of Research

Case Report

Cefdinir induced Syndrome of Inappropriate Release of Antidiuretic Hormone

Ogbonna S[1], Havill J[2]

[1]NHRMC Internal Medicine Residency Program, Wilmington, NC, USA
[2]Eastern Nephrology Associates, Wilmington, NC, USA



Correspondence

John Havill

Eastern Nephrology Associates, Wilmington, NC, USA

- Received Date: 25 June 2024
- Accepted Date: 04 July 2024
- Publication Date: 06 July 2024

Keywords

Hyponatremia, cefdinir, SIADH, syndrome of inappropriate antidiuretic hormone

Abstract

Antidiuretic hormone (ADH) is secreted by the posterior pituitary gland. Unsuppressed release of ADH leads to hyponatremia. This condition is referred to as syndrome of inappropriate antidiuretic hormone secretion (SIADH). Here we present the first case report of cefdinir-induced SIADH. A 76 year-old male was prescribed cefdinir for a urinary tract infection. Two days later he fell and sustained a fracture of C1, his sodium was notably 128 mmol/L. Seven days later he presented again to the emergency room with generalized weakness, headaches, and decreased appetite and was found to have a sodium level of 116 mmol/L. Serum osmolality was appropriately decreased at 243 mOsmol/kg, urine osmolality was not maximally dilute at 422 mOsmol/kg, and urine sodium was 94 mmol/L. On presentation, cefdinir was held and he received ceftriaxone for the first 48 hours of his admission, after which this was also stopped. He was treated with urea powder and received one dose of tolvaptan with progressive improvement in sodium levels allowing for discharge. On post exposure day 27 serum sodium level normalized (142 mmol/L), without the need for urea powder and all symptoms resolved.

This is the first reported case of SIADH associated with cefdinir though there have been scant case reports [1] of cephalosporins causing SIADH.

Introduction

Vasopressin or antidiuretic hormone (ADH) is secreted by the posterior pituitary gland after synthesis in the hypothalamus. ADH regulates distal tubular reabsorption of water by inducing synthesis of water transport proteins (aquaporin mediated via the V2-receptor) [2], thereby promoting increased water reabsorption and increasing urine concentration. The syndrome of inappropriate antidiuretic hormone secretion (SIADH) is characterized by an excess of intravascular water and subsequent dilution of sodium, accompanied by inappropriately elevated urine osmolality. The severity of SIADH depends on the speed of onset and the degree of hyponatremia - mild with serum sodium ranging from 130 to 135 mmol/L, moderate with serum sodium ranging from 125 to 129 mmol/L, and severe with serum sodium less than 125 mmol/L [3]. Symptoms of hyponatremia depend on the severity and include anorexia, nausea, headaches, irritability, drowsiness, confusion, seizures, and coma.

SIADH has itself a broad differential and includes medications, cancers, lung disease, surgery, and general anesthesia. The classic seminal article describing the Bartter-Schwartz criteria [4] are used to make a diagnosis of SIADH, include serum sodium level less than 135 mmol/L, serum osmolality less than 275 mOsm/kg, urinary sodium level more than 30 mmol/L, and urine osmolality >100 mOsm/L. The diagnosis also requires exclusion of volume depletion, and exclusion of other potential causes of hyponatremia, including recent use of diuretic drugs, adrenal insufficiency and hypothyroidism.

We present the first case report of a gentleman who developed severe SIADH after initiating cefdinir for the treatment of a urinary tract infection.

Case Presentation

A 76 year old gentleman presented to his local emergency room with dysuria and urinary incontinence. He was prescribed cefdinir for urinary tract infection (UTI). Despite this, his family stated that he continued to do quite poorly, sustaining a fall with a fracture of C1 requiring placement of a cervical collar 2 days later (day 3 post exposure). He required a 48 hour hospitalization, during cefdinir was held and he received ceftriaxone, however, at discharge cefdinir was re-initiated. During this hospitalization his sodium was notably 128 mmol/L.

On day 10 post exposure, his family brought him to our facility for further evaluation for symptoms of weakness, anorexia and headache. He was found to have a serum sodium of 116 mmol/L. At the time of hospitalization his

Citation: Ogbonna S, Havill, J. Cefdinir induced Syndrome of Inappropriate Release of Antidiuretic Hormone. Japan J Res. 2024;5(5):039.

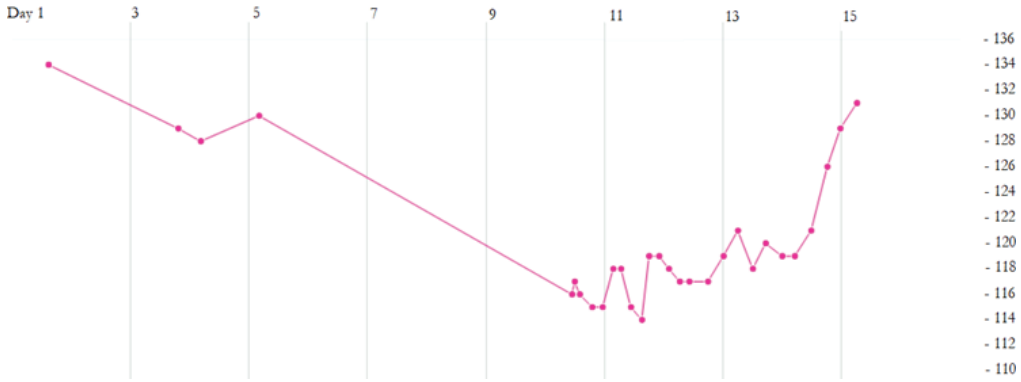


Figure 1. *Graphical representation of sodium (mmol/L) trend throughout hospitalizations.*

urine osmolality was 422 mmol/L, urine sodium of 94 mmol/L, urinalysis had demonstrated a small amount of ketones but no urinary protein. His serum osmolality was appropriately low 243 mOsm/kg and TSH was 0.765 mU/L.

His home medications included lisinopril, however, they specifically denied exposure to opioids, antidepressants, anti-seizure therapy, thiazide diuretics. No exposure to steroid therapy. On examination he was clinically euvolemic. His family reported encouraging fluid intake after he was diagnosed with a UTI although the volume was vague. No alcoholic beverages were reported.

Over the first 3 days of hospitalization (post exposure days 10-13), he received sodium chloride 2 g p.o. 3 times daily with intermittent doses of furosemide. Despite these measures the serum sodium changed very little, improving to only 119 mmol/L. Cefdinir was held and he received ceftriaxone therapy for 3 days after this was also stopped. On the fourth day of hospitalization (post exposure day 14), urea powder 15 g twice a day was initiated. Tolvaptan was administered after serum sodium increased to 121 mmol/L on the 5th day. CT scan of the lungs demonstrated biapical scarring and mild centrilobular pulmonary emphysema with no nodular lesions/interstitial lung disease. On the sixth day (post exposure day 16), his serum sodium increased to 131 mmol/L with resolution of all symptoms, at time he was discharged on urea powder 15 g twice a day.

He continued urea powder for 1 week following his discharge (until post exposure day 22) after it was stopped. On day 20 his sodium was 138 mmol/L. One week later, on day 27, serum sodium was 142 mmol/L.

He took lisinopril for many years, continuing lisinopril throughout hospitalization and during subsequent visits to the outpatient clinic.

The onset of hyponatremia in this case appears to be related to the administration of cefdinir. He suffered a fall and sustained a fracture of C1. Disequilibrium complicated by falls are an appreciated consequence of hyponatremia [3]. His underlying emphysema and use of lisinopril may have increased his predisposition to SIADH as they are known causes [4], however, having preceded and followed this episode, were obviously not the acute trigger.

Table 1. *Table of admission work up on post exposure day 10*

Laboratory	Value
Serum sodium	116 mmol/L
TSH	0.765 mIU/L
Urine Osmolality	422 mOsm/Kg
Urine sodium	94 mmol/L

Discussion

The case presented describes an elderly male who developed severe SIADH complicated by disequilibrium and fall after initiating cefdinir for the treatment of a urinary tract infection. He had predisposing factors including emphysema and lisinopril, that had previously not resulted in hyponatremia. His presenting biochemistry was consistent with a diagnosis of SIADH including appropriately low serum osmolality, non-maximally dilute urine, elevated urine sodium. This episode temporally correlated with his exposure to this drug in regard to its onset and resolution. We used a variety of agents during the episode to expedite recovery including sodium chloride tablets, furosemide, urea powder and a single dose of tolvaptan.

Cefdinir has been available since 1997. It is a third generation cephalosporin, treating a variety of gram negative and gram positive bacterial infections including skin, lungs, ears, sinuses and as in our case, the urine. It's chemical structure allows it to be effective against organisms that are resistant to first line cephalosporins given the production of beta-lactamase enzymes [5,6].

Third generation cephalosporins cross the blood-brain barrier and are found in high concentrations in the cerebrospinal fluid. This drug is predominantly renally excreted. Dose adjustments may be required for patients with renal impairment or on dialysis [7]. Crossing the blood-brain barrier offers a possible mechanism by interference with hypothalamic function may occur.

Common adverse effects of cefdinir include diarrhea, nausea, abdominal pain, headaches, shortness of breath and melena. Hyponatremia has not been identified as a side effect to cefdinir and very few case reports of association with cephalosporins in general. There has been one case report of a 70-year-old woman who developed hyponatremia while on an intravenous course of cefoperazone/sulbactam on two separate occasions [1]. Cefoperazone is a third-generation cephalosporin, is combined with a beta-lactamase inhibitor, sulbactam. Considering cefdinir has a similar mechanism of action with beta lactamase, should raise suspicion to the possible cause of hyponatremia.

It is a limitation of case reports, that causality cannot be established, and so our intention with this report is to simply highlight a possible association, for clinicians should be mindful of in the future. With this case report we hope to alert the field to this possibility, so that, if cases emerge in the future they will be recognized and reported.

References

1. Mitra S, Basu S. Cefoperazone / sulbactam induced hyponatremia. Indian J Med Sci. 2006;60(4):158-9.
2. Wilson JLL, Miranda CA, Knepper MA. Vasopressin and the Regulation of Aquaporin-2. Clin Exp Nephrol. 2013; 17(6): 10.1007/s10157-013-0789-5.
3. Renneboog B, Musch W, Vandemergel X, Manto MU, Decaux G. Mild chronic hyponatremia is associated with falls, unsteadiness, and attention deficits. Am J Med. 2006;119(1):71.e1-8.
4. Bartter FC, Schwartz WB. The syndrome of inappropriate secretion of antidiuretic hormone. The American Journal of Medicine. 1967;42(5):790-806.
5. Perry CM, Scott LJ. Cefdinir: a review of its use in the management of mild-to-moderate bacterial infections. Drugs. 2004;64(13):1433-64.
6. PubChem [Internet]. Bethesda (MD): National Library of Medicine (US), National Center for Biotechnology Information; 2004-. PubChem Compound Summary for CID 6399253, E-Cefdinir; [cited 2024 June 12]. Available from: https://pubchem.ncbi.nlm.nih.gov/compound/E-Cefdinir
7. Charles G. Prober. Cephalosporins: An Update. Pediatr Rev. 1998;19 (4): 118–127.