SIADH Associated With Ciprofloxacin

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Sultan M. Babar, MD[1]

Abstract

Objective: To report a case of ciprofloxacin-induced syndrome of inappropriate antidiuretic hormone (SIADH). **Case Summary:** A 68-year-old Caucasian woman presented on 2 separate occasions with generalized weakness. Both times, she was started on ciprofloxacin for a urinary tract infection. Prior to the first episode, she had also been on Augmentin for several days. On both occasions, her ciprofloxacin was discontinued on admission, and her sodium levels rose. On the first occasion, she was given 5% dextrose in water to slow the rate of rise, yet she still corrected faster than the recommended rate. After the second admission, she was briefly given hypertonic saline but remained off intravenous fluids, and her sodium again rose faster than the recommended rate. **Discussion:** An objective causality assessment using the Naranjo scale was done. A score of 8 revealed a probable causality between ciprofloxacin and SIADH. The likely mechanism of this reaction is ciprofloxacin crossing the blood-brain barrier and stimulating the γ-aminobutyric acid and N-methyl-D-aspartate receptors, which leads to the synthesis and release of antidiuretic hormone. **Conclusion:** Fluoroquinolones have the potential to cause SIADH. In this case, ciprofloxacin probably caused SIADH.

Keywords

SIADH, hyponatremia, fluoroquinolone, ciprofloxacin

Introduction

Antidiuretic hormone (ADH), also referred to as vasopressin, is secreted by the neurophysis to increase the reabsorption of water.[1] It has a half-life of about 16 to 24 minutes.[2,3] Syndrome of inappropriate antidiuretic hormone (SIADH) is a condition in which the body's ADH levels are inappropriately high and lead to increased reabsorption of water and decreased plasma osmolality.[4] It is important to recognize and diagnose SIADH because of its serious implications. The severity of the symptoms usually correlates with the degree of hyponatremia: patients above 130 mEq/L tend to be asymptomatic.[5] The clinical presentation when sodium levels are below 130 mEq/L may include anorexia, nausea, vomiting, abdominal pain, and severe adverse neurological effects, such as seizures and coma, especially when the presentation level is below 115 mEq/L.[5] The diagnostic criteria for SIADH include hypotonic hyponatremia, urine osmolality >100 mOsm/kg, absence of extracellular volume depletion, and normal thyroid, adrenal, cardiac, hepatic, and renal function.[6]

In cases of chronic hyponatremia, care should be taken not to correct it too quickly. The rapid correction of hyponatremia can lead to central pontine myelinolysis (CPM).[7]

Ciprofloxacin is a second-generation fluoroquinolone and the most potent fluoroquinolone against Gram-negative bacteria.[8] Common adverse drug reactions include central nervous system effects, gastrointestinal symptoms, skin rashes and allergic reactions, phototoxicity, cartilage damage, tendinitis, and minor renal and hepatic syndromes.[8]

This report addresses the case of a 68-year-old Caucasian woman who was admitted to the hospital on 2 separate occasions with SIADH that was diagnosed after she was started on ciprofloxacin. There have been a few cases of SIADH reported with fluoroquinolones, but to the author's knowledge, this is the only report that documents the rate of correction and links it to the removal of the offending fluoroquinolone.

Case Report

In 2008, a 68-year-old Caucasian woman presented to the emergency department (ED) with a medical history of hypertension, hypercholesterolemia, atrial fibrillation, and gastroesophageal reflux disease. In addition to the ciprofloxacin (500 mg twice daily), she was on atorvastatin (40 mg daily), diltiazem sustained release (360 mg daily),

[1]East Carolina University, Greenville, NC, USA

Corresponding Author:
Sultan M. Babar, Brody School of Medicine/Department of Family Medicine, East Carolina University, 600 Moye Blvd, Greenville, NC 27834-4300, USA.
Email: babarsu@ecu.edu

Table 1. List of Medications the Patient Was Taking at the Time of Her Presentation.

2008	2012
Ciprofloxacin 500 mg twice a day	Ciprofloxacin 500 mg every 12 hours
Atorvastatin 40 mg daily	Atorvastatin 40 mg daily
Diltiazem sustained release (SR) 360 mg daily	Diltiazem SR 360 mg daily
Esomperazole 40 mg daily	Esomperazole 40 mg daily
Losartan 100 mg daily	Losartan hydrochlorothiazide 100-12.5 mg daily
Coumadin 4 mg daily	Coumadin 4 mg daily
	Hydralazine 25 mg 3 times a day
	Sotalol 80 mg twice a day

esomeprazole (40 mg daily), losartan (100 mg daily), and Coumadin (4 mg daily). All medications were taken orally (Table 1). She had a past surgical history of cholecystectomy.

Approximately 2 weeks prior to presentation, she had been diagnosed with a sinus infection. She was prescribed Augmentin for 10 days. The patient complained that she started feeling "weak" and "generally bad"; she started having nausea, vomiting, and diarrhea. Three days later, she went to her primary care physician (PCP), and based on her symptomatology and a urinalysis (UA), she was diagnosed with a urinary tract infection. She was started on ciprofloxacin, and Augmentin was discontinued. No other changes had been made to her medication in the prior 6 months.

Her nausea and vomiting continued to worsen, and she presented to the ED for an evaluation. She reported being slightly fatigued and tired and denied seizures, headaches, and falls. On exam, she was alert and oriented to person, place, and time. There was no edema; her breath sounds were clear, and she had moist mucous membranes. Her blood pressure was 142/75 with a pulse of 95 with an irregular rhythm.

In the ED, her labs were significant for the following: sodium (104 mEq/L), serum osmolality (221 mOsm/kg), urine osmolality (236 mOsm/kg), blood urea nitrogen (BUN; 16 mg/dL), and creatinine (0.49 mg/dL).

Her UA on admission showed no signs of infection, and ciprofloxacin was discontinued. Given her hyponatremia of unknown chronicity, she was admitted, and her sodium was monitored. It was decided that to prevent CPM, her sodium would be corrected by about 10 mEq/L in the first 24 hours and by 18 mEq/L in the first 48 hours.[8] It was noted that her sodium was rising faster than anticipated, and she was given hypotonic fluids to slow the rate of increase. Despite receiving hypotonic fluids, her sodium rose to 125 mEq/L within 48 hours (Figure 1). She was in the hospital for 8 days, and her sodium continued to improve: it was at 133 mEq/L on discharge.

In 2012, she returned to her PCP with complaints of dysuria, and after a UA, she was diagnosed with a urinary tract infection and started on ciprofloxacin (500 mg every 12 hours). Then, 3 days later, she returned to her PCP complaining of symptoms similar to her last hyponatremic episode: general fatigue and feeling slower than usual. She requested that her PCP check her sodium. The next morning, she received a call from her PCP that her sodium was at 108 mEq/L and she was instructed to go to the ED.

In the ED, she reported that she had been feeling weaker since she was started on ciprofloxacin and that she had been getting progressively weaker. On exam, she was noted to have slowed speech, but she was alert and oriented. Her finger to nose test did not elicit a tremor but was noted to be slow and symmetric bilaterally. Her neurological exam was symmetrical and did not have any focal findings. Her blood pressure was 144/50, with a pulse of 108 with an irregular rhythm.

Her other medications were atorvastatin (40 mg daily), Coumadin (4 mg daily), diltiazem sustained release (360 mg daily), esomeprazole (40 mg daily), hydralazine (25 mg 3 times a day), losartan-hydrochlorothiazide (100-12.5 mg daily), and sotalol (80 mg twice daily). All medications were taken orally (Table 1). Her diltiazem had been decreased to 240 mg in the past when she was started on sotalol, but the exact date of this was unknown. She reported that a week prior to admission, her diltiazem had been increased to 360 mg. Her pertinent labs were as follows: sodium (109 mEq/L), serum osmolality (222 mOsm/kg), urine osmolality (251 mOsm/kg), BUN (8 mg/dL), and creatinine (0.51 mg/dL).

Because she was symptomatic for hyponatremia, she was started on 3% NaCl at 30 mL/h. After about 50 minutes, her sodium was found to be correcting too quickly, and she was at risk for CPM. After about 25 mL of 3% NaCl, her hypertonic saline was stopped. For the remainder of her stay, she did not get any intravenous fluids (IVFs). She was in the hospital for 3 days, and her sodium corrected to 133 mEq/L. Her sodium again corrected faster than the recommended rate[8] (Figure 2).

During her hospitalization, all her medications except ciprofloxacin were continued at the doses she had been taking at home.

Discussion

This 72-year-old woman presented with a repeated occurrence of SIADH following reexposure to ciprofloxacin. The patient was hyponatremic and hypotonic, her serum

osmolality was lower than her urine osmolality, she continued natriuresis, there was no edema or signs of dehydration on physical exam, and her BUN and creatinine were normal and at her baseline on both admissions. Although her cortisol was not checked during the first stay, it was found to

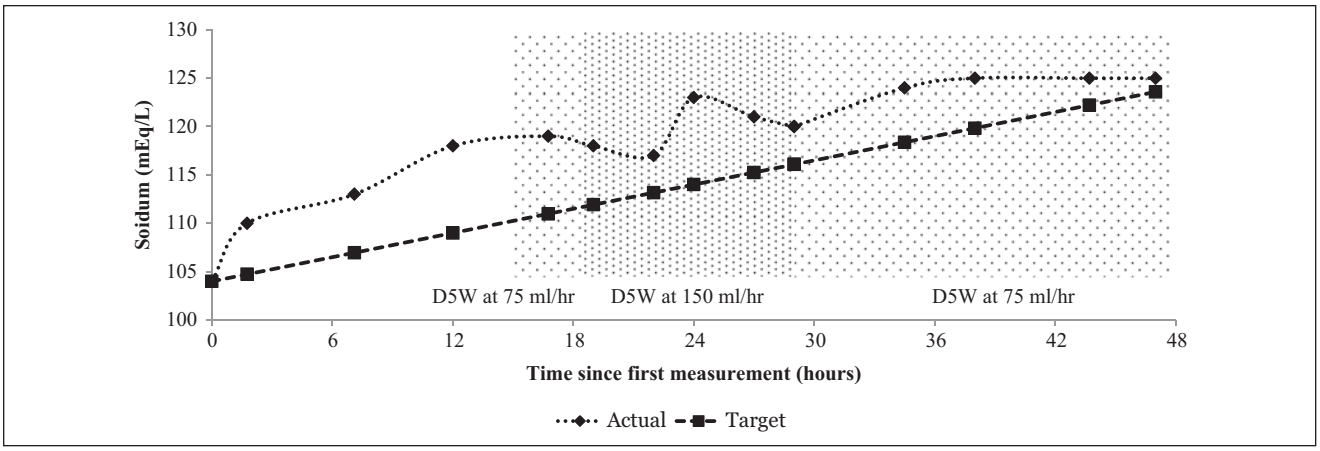

Figure 1. Graph of sodium levels from the 2008 admission, 48 hours after first check.
Abbreviation: D5W, 5% dextrose in water.

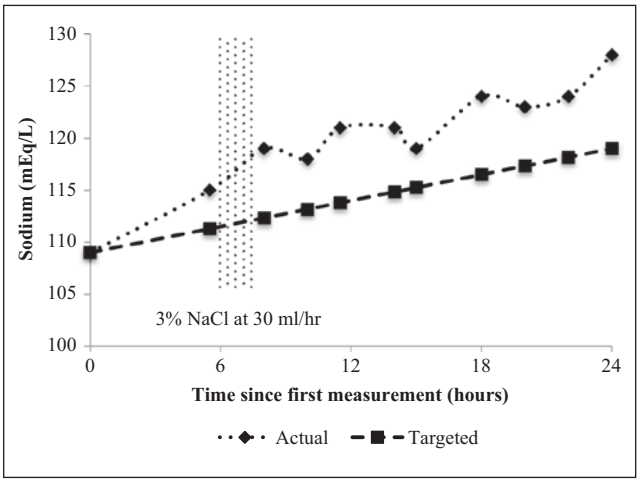

Figure 2. Graph of sodium levels from the 2012 admission, 24 hours after first check.

be normal during the second stay; her thyroid stimulating hormone level was normal on both occasions (Table 2).

Even though she met criteria for SIADH on both occasions, we noted some differences in her treatment between admissions.[2,6] Ciprofloxacin was stopped on both admissions, but the amount and type of IVFs she received differed. On first admission, she received 5% dextrose in water (Figure 1), and on second admission she briefly received 3% NaCl (Figure 2). In another reported case, the offending fluoroquinolone was not removed, and the patient received IVFs. In that case, the patient's sodium reached a plateau at below-normal levels.[9] It was only after the discontinuation of the offending agent that a correction of hyponatremia was seen.[9] Therefore, the mainstay of treatment is the discontinuation of the offending agent and not the use of IVFs. Furthermore, as highlighted in Figure 1, between hours 18 and 26 she received 5% dextrose in water at 150 mL/h, and yet her sodium was still rising. This indicates that once the offending agent is removed, the hyponatremia will correct despite a high rate of hypotonic IVFs.

The Naranjo algorithm was used to evaluate the likelihood that the SIADH was caused by ciprofloxacin.[10] The resulting score was 8, indicating a probable adverse drug reaction. There have been 3 other published cases of SIADH associated with fluoroquinolones, 1 with ciprofloxacin and 2 with moxifloxacin.[9,11,12] In this case, the symptoms started after ciprofloxacin administration in 2012, although the timeline is not as clear in the 2008 incident. SIADH corrected after the drug was discontinued. We ruled out all other common causes of SIADH, including hyperglycemia, adrenal insufficiency, thyroid disorder, and malignancy. Additionally, the patient did have a history of a similar reaction with ciprofloxacin. Serum sodium is an objective measurement.

There were potential confounders in both presentations. In 2008, she was on Augmentin before she was started on ciprofloxacin; in 2012, she was concurrently taking a thiazide diuretic, and her 25 pack-year smoking history made malignancy a possible explanation of her SIADH. Augmentin was present only in the first presentation. Her thiazide diuretic was continued on admission. Her chest X ray was negative, and given the rapid resolution following the discontinuation of ciprofloxacin, it is very unlikely that an undiscovered malignancy was the underlying issue.

A review of published cases show that the age range of these patients was between 66 and 73 years.[9,11,12] Duration of exposure varied from 2 days to 1 week. Serum sodium ranged from 104 to 113 mEq/L, and serum osmolality ranged from 221 to 265 mOsm/kg.[9,11,12] (Table 2).

Ciprofloxacin is lipophilic and can cross the blood-brain barrier.[13] There are in vitro data indicating that fluoroquinolones have the potential to bind to γ-aminobutyric acid and N-methyl-D-aspartate receptors.[9,14] It has also been shown that γ-aminobutyric acid and N-methyl-D-aspartate receptor stimulation plays a role in ADH synthesis and release.[9,15]

Table 2. Comparison of Reported Cases of Fluoroquinolone-Associated SIADH.

	2008	2012	Yam and Eraly[9]	2001, Adler et al[11]	2003, Adler et al[11]	Mussig et al[12]
Patient Age/Gender	68 Years/female	72 Years/female	66 Years/female	68 Years/male	70 Years/male	73 Years/female
Serum sodium (mEq/L)	104	109	110	113	113	108
Serum osmolality (mOsm/kg)	221	222	240	241	265	230
Urine osmolality (mOsm/kg)	236	251	348	426	324	525
Urine sodium (mEq/L)	49	30	27	50	86	Not reported
TSH (μIU/mL)	0.85	0.52	Not reported	Not reported	Not reported	Not reported
Serum glucose (mg/dL)	138	112	Not reported	Not reported	Not reported	Not reported
Level of am cortisol (μg/dL)	Not done	11.7	Not reported	Not reported	Not reported	Not reported
Medication	Ciprofloxacin	Ciprofloxacin	Moxifloxacin	Ciprofloxacin	Ciprofloxacin	Moxifloxacin
Dose frequency	500 mg bid	500 mg q12h	400 mg daily	Not reported	500 mg bid	400 mg daily
Duration of exposure	2 days	3 days	1 week	Not reported	5 days	3 days

Abbreviations: SIADH, syndrome of inappropriate antidiuretic hormone; TSH, thyroid-stimulating hormone; q12h, every 12 hours

Given this, the likely mechanism through which ciprofloxacin causes SIADH could be by stimulating the release of ADH from the central nervous system. Given the short half-life of ADH, removal of the offending agent can lead to a rapid drop in ADH levels.[2,3] Normalization of the ADH level allows the normal physiological homeostasis to correct the hyponatremia rapidly. This rapid correction was seen in this case, and it supports the proposed mechanism of action.

Conclusion

There have been several cases that have linked SIADH with fluoroquinolones—ciprofloxacin and moxifloxacin. These cases have, so far, been reported in those older than 66 years. Given previous cases and the Naranjo scale score of 8 in this report, it can be concluded that ciprofloxacin probably has the potential to cause SIADH. Although the number of cases is not large enough to come to a definitive conclusion, this risk might be higher in elderly patients.

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