A Case of Flecainide-Induced Hyponatremia

Abstract

The complex classification for the diagnosis and treatment illustrates that hyponatremia is a very heterogeneous disorder. However, data on hyponatremia induced by flecainide, an often-prescribed antiarrhythmic agent, are scarce in the literature. A 78-year-old man with a recent history of recurrent hyponatremia and symptomatic paroxysmal atrial fibrillation presented with the complaints of dizziness and fatigue. During his repeated hospital admissions, the patient was treated with hypertonic saline, which temporarily improved serum sodium levels, but hyponatremia recurred without sustained clinical improvement. After discontinuation of the drug, the sodium levels remained stable. Doctors should be aware of not only the electrocardiographic changes associated with flecainide, but also the less-often found clinical manifestations linked with hyponatremia.

Keywords: *Flecainide, hyponatremia, paroxysmal atrial fibrillation*

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Introduction

Hyponatremia, defined as a serum sodium [Serum Na] <136 mmol/L is the most common disorder of water homeostasis in hospitalized patients and often a diagnostic and therapeutic challenge.[1] The diagnosis of hyponatremia is underestimated and its management is still problematic.[2] Hyponatremia seems to be a heterogeneous pathophysiologic disorder rather a disease itself.[3] That is why "the" patient with hyponatremia does not exist, but the underlying disease that is complicated by hyponatremia.[4] Flecainide acetate is an antiarrhythmic agent used as one of the first-line therapies for pharmacological conversion as well as maintenance of sinus rhythm in patients with atrial fibrillation and supraventricular tachycardia.[5,6] We present a case with symptomatic hyponatremia attributed to prescribed flecainide. The case was difficult to resolve due to comorbidity and highlights the existence of flecainide-induced hyponatremia.

Case Report

A 78-year-old male, conscious and oriented, with a recent history of hyponatremia and symptomatic paroxysmal atrial fibrillation (PAF) presented to our emergency room with dizziness and fatigue after his cardiologist's referral to the hospital. Initial vital signs included a heart rate of 50 bpm and a blood pressure of 110/80 mmHg. Laboratory values upon admission included serum sodium of 127 mmol/L, serum potassium of 4.5 mmol/L, and serum creatinine of 1.24 mg/dL. Biochemical urine test showed urine specific gravity of 1009 and unremarkable test urine profile.

The patient had a recent history of symptomatic hyponatremia and episodes of PAF for several months, documented on his several admissions during the last 3 months. Initially, the patient with a history of PAF presented to the local emergency department with palpitations, dizziness, and near syncope following a fall. He was found with PAF, which restored automatically, and was treated conservatively with an antiarrhythmic (amiodarone), an antihypertensive (lisinopril), a heart rate control (nebivolol), and blood clot and stroke prevention medication (rivaroxaban). During his stay, he developed hyponatremia. Antidiuretic hormone and cortisol were measured and found to be within normal ranges. The patient was referred for neurosurgical evaluation due to the recent history of fall, and a subdural hygroma was revealed by magnetic resonance imaging (MRI). Serum

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Na remained low (121 mg/dL) and was attributed to head injury, while high thyroid stimulating hormone (TSH) level (5.6 mIU/L; normal range 0.4–5.2 mIU/L) was attributed to the recent use of amiodarone. Patient switched to acetate flecainide at a dose of 50 mg per twice a day for the prevention of PAF in accordance with the estimating Glomrular Filtration Rate level. During follow-up, low Serum Na (127 mmol/L) and dizziness were still present. Patient was treated with hypertonic saline and the sodium level normalized to 138 mmol/L. At his discharge, lisinopril was substituted with amlodipine, possibly as a cause of his hyponatremia.

In less than a month, the patient presented to our emergency department (Day 1) with the complaints of dizziness and fatigue suggestive of symptomatic chronic hyponatremia because of persisting low Serum Na level and high urine sodium (UNa) level (>40 mmol/L). Patient was admitted to the hospital due to walking instability and moderate bradypsychia and was treated with hypertonic saline. Initial treatment included water intake of 1 L orally, quitting intravenous saline fluids, and continuing patient's medication. Overall, the patient was hypo- to euvolemic, with low serum osmolality (275 mOsm/kg H_2O), no use of diuretics, and no hyperkalemia or acid base disorders. Creatinine clearance was measured at 50 mL/min/1.73 m^2 (Chronic Kidney Disease stage 3a). However, serum Na started to fall again (Day 8), while urinary Na was still high (with normal dietary sodium intake 5–7 g/day).

In differential diagnosis, syndrome of inappropriate antidiuresis (SIAD) or cerebral salt wasting (CWS), as result of head trauma or undiagnosed cancer, and abnormal thyroid or adrenal function were at first considered as culprits. Thyroxine at a concentration of 12.5 µg was added as indicated from his clinical presentation (fatigue and low energy). Antidiuretic hormone and cortisol were measured again and found to be within normal ranges. Also, computed tomography (CT) head and thorax/abdomen were conducted and they showed no abnormal findings. The hygroma had subsided since 2 months ago. Serum Na (Day 12) could not reach the normal range despite thyroxine administration combined with flecainide. So, CSW could be a cause and/or based on recent drug history, the use of flecainide could be another cause.

Drug's blood levels could not be measured and we proceeded to test the hypothesis of flecainide-induced hyponatremia, which is not referred to drug's specific product characterization (SPC) leaflet. Flecainide was stopped (Day 12) and dietary sodium intake increased (till 12 g/day), in coordination with the patient's cardiologist. After his discharge, the serum Na was raised to 144 mmol/L (Day 20) and reduced dietary intake of sodium was recommended. At Day 30, flecainide was resumed, and 10 days later, the serum Na levels fell again to 129 mmol/L**.** Transthoracic echocardiogram was conducted twice after his fall, which showed normal reference ranges and stable ejection fraction (EF = 55%). Flecainide was switched to sotalol and the serum Na rose to 139 mmol/L (Day 50). The serum Na levels remained stable (138 mmol/L) during the upcoming month (Day 80), as shown in Table 1. Despite advice for a normal salt intake, the patient maintained a high salt diet for fear of reoccurrence of symptoms.

Discussion

Hyponatremia appears occasionally as a side effect of drugs commonly used in clinical practice.[7] In our case, differential diagnosis was hindered by the coincidence of events. At first, head injury was thought to be the culprit, but hygroma subsided. But hyponatremia persisted and the patient was admitted twice to the emergency department. Imaging and laboratory values did not justify SIAD, CSW, thyroid or adrenal dysfunction as the cause of chronic hyponatremia. Clinical suspicion of drug-induced hyponatremia prompted us to stop andstart trial of the use of flecainide. This resulted in the instructive case of the side effect of the drug.[8]

Shahid *et al*. followed 663 hospitalized patients for 29 months and found the incidence of serum sodium

Table 1: Laboratory work-up

	Day 1	Day 3	Day 6	Day 8	Day 10	Day 12 FS	Day 20	Day 30 F R	Day 40 S	Day 50	Day 80	Day 180
SNa	127	128	131	129	126	130	144	139	129	139	138	139
SK	4.8	4.6	4.3	4.8	4.8	4.9	4.8	4.2	4.88	4.7	4.08	4.0
Hb	13.2	13.4	14	14	14	14	14	13.5			12.5	13
Urea	33	44	43	50	50	48	51	42		45	46	47
Cr	1.24	1.21	1.34	1.4	1.4	1.34	1.29	1.11		1.10	1.12	0.94
CRP	0.4		0.8								0.1	
UNa/24 h		133	196	106	97	85	240	234	235	226	201	232
UVol/24 h		1600	1500	1060	1150	1050	1600	1500	1400	1650	1400	1750
TSH		5.6										3.54

Cr=creatinine (mg/dL), CRP=C-reactive protein (mg/L), FS=flecainide withdrawal, FR=flecainide restart, Hb=hemoglobin (g/dL), S=switch to sotalol, SK=serum potassium (mmol/L), SNa=serum sodium (mmol/L), TSH=thyroid stimulating hormone (µIU/mL), UNa=urine sodium (mmol/L), UVol=urine volume (mL)

reduction with flecainide use during hospital stay to be 8.9%.[9] Female gender, older age, and concomitant use of diuretics were the risk factors. Furthermore, flecainide-induced hyponatremia has the potential to cause life-threatening arrhythmias, including loss of pacemaker capture, even with therapeutic flecainide levels.

Flecainide acetate is a class 1C antiarrhythmic agent indicated for both the pharmacological conversion as well as maintenance of sinus rhythm in patients with atrial fibrillation and supraventricular tachycardia.[10] Flecainide delays phase 0 depolarization of the cardiac action by binding to $Na_v1.5$ cardiac sodium channels, causing decreased contractility of the muscle.[11] The sodium channels are also localized in the distal colon and in the renal tubules, suggesting antagonism of flecainide either in the distal nephron and cortical collecting duct or in the colon epithelial sodium channels, inhibiting sodium absorption and chloride secretion.[12] The current literature on the pharmacodynamics of flecainide does not establish a common pathway of the drug on the sodium channels at different sites, which is a probable cause for drug-induced hyponatremia.

Conclusion

This case illustrates some key points. Recognition of side effects is important to establish diagnosis protocol and avoid unnecessary treatment. Flecainide can be safely used in patients with normal renal function, but with caution in elderly with reduced renal function. Doctors should be aware of the clinical manifestations of hyponatremia linked with drug's toxicity. Finally, we recommend regular sodium monitoring to avoid the undesirable side effects of flecainide.

Statements

All papers must contain the following statements after the main body of the text and before the reference list.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Statement of ethics

Patient's consent was obtained.

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Conflicts of interest

There are no conflicts of interest.

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