

Hyponatremia – A Rare but Serious Complication of Amiodarone: A Case Report and Review of the Literature

Linh Pham^a Andrea J. Shaer^a Thomas Marnejon^{a, b}

^aDepartment of Medicine, St. Elizabeth Health Center, Youngstown, Ohio, and

^bDepartment of Medicine, Northeast Ohio Medical University, Rootstown, Ohio, USA

Key Words

Amiodarone · Hyponatremia · Syndrome of inappropriate antidiuretic hormone secretion · Side effect

Abstract

Introduction: Hyponatremia secondary to the syndrome of inappropriate antidiuretic hormone secretion (SIADH) during amiodarone therapy is a rare but potentially lethal adverse effect. We report a case of severe hyponatremia associated with amiodarone, and discuss its clinical implications. **Case Report:** An 84-year-old Caucasian man with a past medical history of hypertension and diabetes was admitted to the hospital with a non-ST elevation myocardial infarction. He underwent coronary artery bypass graft and developed atrial fibrillation on postoperative day 2. A loading dose of amiodarone followed by a maintenance dose was started. The serum sodium level was 136 mmol/l at discharge and subsequently decreased to 105 mmol/l 11 days later, at which time the patient represented with altered mental status. The diagnosis of SIADH was made based on euvoletic hyposmotic hyponatremia, lack of any other medication known to cause SIADH and urine that was less than maximally dilute. The serum sodium increased gradually to 123 mmol/l after 36 h of treatment with hypertonic saline, demeclocycline and fluid restriction. **Conclusion:** SIADH-induced hyponatremia associated with amiodarone occurs rarely. Since severe hyponatremia is associated with significant neurological damage and mortality, clinicians should carefully monitor serum sodium during amiodarone therapy.

Thomas Marnejon, DO
Department of Medicine, St. Elizabeth Health Center
1044 Belmont Avenue
Youngstown, OH 44504 (USA)
E-Mail thomas_marnejon@hmis.org

Introduction

Amiodarone is an effective antiarrhythmic agent with well-known noncardiac toxicities including pulmonary fibrosis, hypo- or hyperthyroidism, liver function abnormalities, corneal deposits and photosensitivity. Hyponatremia secondary to the syndrome of inappropriate antidiuretic hormone secretion (SIADH) during amiodarone therapy is a rare but potentially lethal adverse effect of this drug. We describe the lowest reported serum sodium level due to amiodarone therapy. We also review the previously reported cases of SIADH-induced hyponatremia secondary to amiodarone and discuss salient clinical implications.

Case Report

An 84-year-old Caucasian man with a past medical history of hypertension and diabetes was admitted to the hospital with a non-ST elevation myocardial infarction. Urgent left heart catheterization showed multivessel disease, and the patient subsequently underwent coronary artery bypass graft. On postoperative day 2, the patient developed atrial fibrillation with rapid ventricular response. He was started on intravenous amiodarone with a loading dose of 150 mg, followed by a continuous infusion of 1 mg/min. After 24 h, intravenous amiodarone was discontinued and switched to 400 mg orally every 8 h. The oral dose of amiodarone was tapered over 7 days to 400 mg daily. The patient's atrial fibrillation converted to normal sinus rhythm after the loading dose of amiodarone. He was discharged on postoperative day 7 on amiodarone 400 mg daily. At the time of discharge, his serum sodium was 136 mmol/l.

The patient then presented to the emergency room 11 days later due to altered mental status, weakness and loss of appetite. He was drowsy but arousable. Physical examination revealed normal vital signs and euvolemic status. There was no orthostatic blood pressure change. A neurological examination showed no focal deficit. Laboratory data revealed a serum sodium level of 105 mmol/l. Renal and liver function tests were normal. Thyroid stimulating hormone and cortisol levels were 0.7 μ IU/ml (normal range: 0.350–5.000 μ IU/ml) and 16 μ g/dl (normal range: 3.09–22.40 μ g/dl), respectively. Serum osmolality was 228 mOsm/kg and urine osmolality was 251 mOsm/kg. It was noted that the patient was on furosemide 20 mg daily prior to his admission. Repeat testing after discontinuation of furosemide revealed a serum osmolality of 256 mOsm/kg and a urine osmolality of 506 mOsm/kg. The fractionated excretion of sodium was greater than 1% and the urine sodium was 124 mmol/l.

The diagnosis of SIADH was made based on euvolemic hypoosmotic hyponatremia, with a urine osmolality greater than the serum osmolality, urine sodium level greater than 40 mmol/l, normal thyroid and adrenal function and the absence of other medications known to cause SIADH. The patient was initially treated with hypertonic (3%) saline. His serum sodium increased gradually to 117 and 123 mmol/l after 36 and 48 h of treatment, respectively. Hypertonic saline was discontinued after 3 days, and demeclocycline was added, together with fluid restriction. The patient's mental status improved and his serum sodium normalized after 10 days of treatment (fig. 1).

Discussion

SIADH was first reported by Schwartz et al. in 1957 [1] in patients with bronchogenic carcinoma and meningitis. In 1971, four cases of chlorpropamide-induced hyponatremia were described by Weissman et al. [2]. Since then, a variety of drugs have been added to the list of drugs that cause SIADH [3].

Amiodarone, a benzofuran derivative, was developed by a Belgian company (Labaz) in 1961 by the chemists Tondeur and Binon as an antianginal drug [4]. A few years later, amiodarone was widely used as an antiarrhythmic drug in Europe and other countries. It was not until the mid-1980s that amiodarone was approved by the FDA as a class III antiarrhythmic agent in the United States. In 1996, the first case of amiodarone-induced hyponatremia was reported [5]. Since then, a total of 10 cases of amiodarone-induced SIADH have been published in the literature (table 1; [6–13]).

The mechanism of SIADH-induced hyponatremia secondary to amiodarone is unclear [11]. It could possibly be due to the independent secretion of arginine vasopressin relative to plasma osmolality, full suppression of secretion of this hormone or mutations of the aquaretic (i.e. water channel regulating) vasopressin receptor [3]. Most medications cause SIADH either by sensitizing the kidneys to antidiuretic hormone, by stimulating the release of antidiuretic hormone or by both [14]. Of note, Shavit and Sherer [11] speculated that amiodarone might induce SIADH by its channel-modulating properties on either renal or neural tissues.

Among the 10 reported cases, the majority of patients were elderly men (8 out of 10) with a median age of 69 years. Age and sex may be contributing factors to amiodarone-induced SIADH. The elderly appear to be particularly at risk for drug-induced SIADH [14]. In a study on 736 cases of selective serotonin re-uptake inhibitor-induced SIADH, 75% of patients were over 65 years of age [15].

The duration of time from the initiation of amiodarone to the development of SIADH varied from 3 days to 6 months in the reported cases. The onset of hyponatremia ranged from day 3 to day 11 in patients who received loading doses of amiodarone. In contrast, hyponatremia occurred at 14 days to 6 months in patients receiving maintenance doses. In 7 cases, the serum sodium level normalized within 7–14 days after discontinuation of amiodarone and fluid restriction. It appears that amiodarone-induced SIADH is more prevalent after a loading dose of the drug. However, because of the long half-life of amiodarone, the cumulative effect on the development of SIADH remains undefined.

Acute, severe hyponatremia (serum sodium <125 mmol/l) has been associated with serious sequelae, including confusion, hallucinations, seizures, coma and respiratory failure leading to death [3]. The degree of hyponatremia in the majority of reported cases of amiodarone-induced SIADH was 110–120 mmol/l. In 2 cases, Paydas et al.'s [10] and our case, serum sodium levels were less than 110 mmol/l (107 and 105 mmol/l, respectively). It is important to note that in hospitalized patients, the mortality was 28% in patients with serum sodium <125 mmol/l and 50% in patients with serum sodium level <115 mmol/l [16]. Therefore, amiodarone-induced SIADH is a rare but lethal adverse effect, which occurs predominantly in elderly patients, who typically have multiple comorbidities, especially cardiovascular diseases, for which the drug is used.

The only definitive treatment of SIADH is the elimination of its underlying cause [3, 14]. In all but 3 cases, amiodarone was discontinued and fluid restriction was instituted. In the remaining cases, the dose was decreased. One patient required hemodialysis due to decreasing serum sodium coupled with the development of altered mental status [12].

To our knowledge, a total of 10 cases of amiodarone-induced SIADH have been reported thus far in the literature. This adverse effect can occur as early as 3 days after receiving a loading dose or as late as 6 months in patients on maintenance doses. Age and male sex appear to be contributing factors. The severity of hyponatremia is directly correlated with increased mortality in the hospitalized patient. Therefore, clinicians should be aware of this important complication when treating patients with amiodarone.

References

- Schwartz WB, Bennett W, Curelop S, Bartter FC: A syndrome of renal sodium loss and hyponatremia probably resulting from inappropriate secretion of antidiuretic hormone. *Am J Med* 1957;23:529–542.
- Weissman PN, Shenkman L, Gregerman RI: Chlorpropamide hyponatremia: drug-induced inappropriate antidiuretic-hormone activity. *N Engl J Med* 1971;284:65–71.
- Ellison DH, Berl T: Clinical practice. The syndrome of inappropriate antidiuresis. *N Engl J Med* 2007;356:2064–2072.
- Deltour G, Binon F, Tondeur R, Goldenberg C, Henaux F, Sion R, Deray E, Charlier R: Studies in the benzofuran series. VI. Coronary-dilating activity of alkylated and aminoalkylated derivatives of 3-benzoylbenzofuran (in French). *Arch Int Pharmacodyn Ther* 1962;139:247–254.
- Munoz Ruiz AI, Calvo Elipe A, Guerrero Vega E, Gorgojo Martinez JJ, Vera Lopez E, Gilsanz Fernandez C: Pancreatitis and inappropriate ADH secretion syndrome associated with amiodarone (in Spanish). *An Med Interna* 1996;13:125–126.
- Aslam MK, Gnaim C, Kutnick J, Kowal RC, McGuire DK: Syndrome of inappropriate antidiuretic hormone secretion induced by amiodarone therapy. *Pacing Clin Electrophysiol* 2004;27:831–832.
- Ikegami H, Shiga T, Tsushima T, Nirei T, Kasanuki H: Syndrome of inappropriate antidiuretic hormone secretion (SIADH) induced by amiodarone: a report on two cases. *J Cardiovasc Pharmacol Ther* 2002;7:25–28.
- Odeh M, Schiff E, Oliven A: Hyponatremia during therapy with amiodarone. *Arch Intern Med* 1999;159:2599–2600.
- Patel GP, Kasiraj JB: Syndrome of inappropriate antidiuretic hormone-induced hyponatremia associated with amiodarone. *Pharmacotherapy* 2002;22:649–651.
- Paydas S, Araz F, Balal M: SIADH induced by amiodarone in a patient with heart failure. *Int J Clin Pract* 2008;62:337.
- Shavit E, Sherer Y: Hyponatremia induced by amiodarone therapy. *Isr Med Assoc J* 2007;9:564–565.
- Singla S, Strobel AL, Deshmukh AJ, Paydak H: Amiodarone-related hyponatremia: rare but potentially lethal. *Am J Ther* 2011, E-pub ahead of print.
- Afshinnia F, Sheth N, Perlman R: Syndrome of inappropriate antidiuretic hormone in association with amiodarone therapy: a case report and review of literature. *Ren Fail* 2011;33:456–458.
- Belton K, Thomas SH: Drug-induced syndrome of inappropriate antidiuretic hormone secretion. *Postgrad Med J* 1999;75:509–510.
- Liu BA, Mittmann N, Knowles SR, Shear NH: Hyponatremia and the syndrome of inappropriate secretion of antidiuretic hormone associated with the use of selective serotonin reuptake inhibitors: a review of spontaneous reports. *CMAJ* 1996;155:519–527.
- Gill G, Huda B, Boyd A, Skagen K, Wile D, Watson I, van Heyningen C: Characteristics and mortality of severe hyponatraemia – a hospital-based study. *Clin Endocrinol (Oxf)* 2006;65:246–249.

Table 1. Summary of the 10 cases of SIADH induced by amiodarone reported in the literature, including the present case

First author	Age/sex	Doses of amiodarone	Lowest sodium level mmol/l	Time to develop hyponatremia	Treatment	Day until serum sodium level normalized
Munoz Ruiz [5]	67/F	NA	110	4 months	D/C	Unknown
Odeh [8]	62/F	300 mg qd	120	6 months	D/C	5 days
Patel [9]	67/M	200 mg qd	117	3 months	Fluid restriction + D/C	3 days
Ikegami [7]	63/M	800 mg qd	119	7 days	Decrease to 100 mg + fluid restriction	28 days
	82/M	200 mg × 7 days and 100 mg qd	121	15 days	Continue 100 mg qd + fluid restriction	14 days
Aslam [6]	72/M	2 g qd	117	5 days	Decrease dose to 200 mg qd	14 days
Shavit [11]	85/M	NA	122	30 days	D/C	A few days
Paydas [10]	58/M	NA	107	5 months	D/C	14 days
Singla [12]	58/M	1,600 mg qd	120	3 days	D/C and dialysis	
Afshinnia [13]	66/M	IV 150 mg bolus then 900 mg drip then 1,200 mg PO qd	116	7 days	D/C	16 days
Pham et al. [this report]	84/M	IV 150 mg bolus + drip, then PO 1,200 mg × 7 days then 400 mg qd	105	11 days	D/C + 3% NaCl × 3 days then fluid restriction + demeclocycline	10 days

qd = Daily; NA = not available; D/C = amiodarone discontinued.

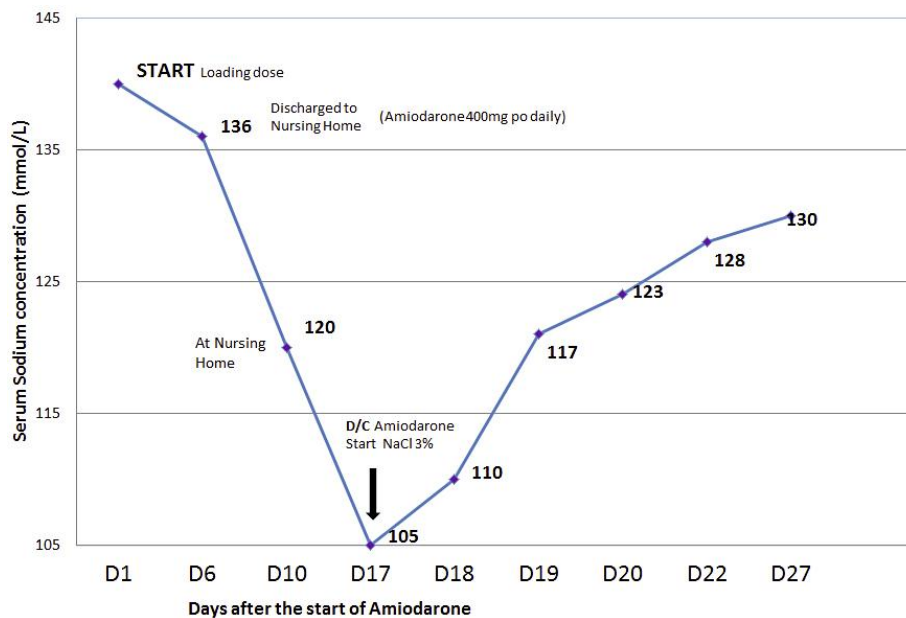


Fig. 1. Change in the serum sodium concentration with time. Note the serum sodium level nadir on day 17.