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# Indapamide-induced hyponatremia or the syndrome of inappropriate antidiuretic hormone secretion: a case report

**Case Report**

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**Abstract:** We report a case of an apparently well-documented indapamide-induced hyponatremia. The initial diagnosis was made on the basis of dechallenge and rechallenge performed on two occasions. Further course of the disease, which proved inconsistent with our expectations, prompted us to look for another aetiology leading to the final diagnosis of the syndrome of inappropriate antidiuretic hormone secretion (SIADH) complicated by indapamide treatment.

**Keywords:** *Hyponatremia • Hypertension • SIADH • Indapamid*



## 1. Introduction

Electrolyte abnormalities in patients receiving diuretics are a natural consequence of therapy. This abnormality results from the mechanism of action of these drugs and is generally taken into account by the doctor at the treatment planning stage. Hyponatremia is a common electrolyte abnormality both in the inpatient and outpatient setting [1]. Hyponatremia is initially oligosymptomatic and, in contrast to hypokalemia, there is no easy way to avoid it. This abnormality may lead to very serious consequences, including brain oedema [2]. Hyponatremia (serum sodium [$Na^+$] < 135 mmol/l) is defined as a relative excess of water relative to sodium in the extracellular space. The extracellular space holds more than 90% of sodium ion contained in the human body [3,4]. Whatever the cause, sodium loss, in contrast to potassium loss, is corrected in this space. Sodium depletion most commonly develops slowly, which gives the body a chance to activate compensatory mechanisms. The symptoms of this slowly developing sodium deficit are scarce and initially completely absent. Patients most commonly report asthaenia, nausea, vomiting, later followed by headache, dizziness and, in most severe cases, loss of consciousness and seizures. Rapidly developing sodium depletion leads to neurological signs and symptoms [3]. One of the most common causes of hyponatremia is the syndrome of inappropriate antidiuretic hormone secretion (SIADH) [1].

## 2. Case Presentation

This case report concerns a 76-year-old male patient, with normal body mass (BMI 24.79 kg/m$^2$), with a 50 year history of smoking, a history of two strokes, one in 2001 and the other in 2003 with subsequent mixed aphasia and trace left-sided hemiparesis, with osteoarthritis, managed for about 10 years for hypertension and gout, with a history of atrial fibrillation episodes and hypnotic

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**Table 1.** Clinically relevant laboratory results.

| Parameter | Values | Normal range | Unit |
|---|---|---|---|
| Plasma osmolality | 278; 275; 273 | 280–300 | mOsm/kg |
| ADH | >30 | 2-6 | ng/l |
| Cortisone | 20.8; 12.4 | 6.2–19.0 | μg/dl |
| Aldosterone | 73.3 | 20-80 | pg/ml |
| ACTH | 5.0 | 4,7-48,8 | pg/ml |
| NT-proBNP | 355 | 0–100 | pg/ml |
| Plasma renin activity | 65.1 | 2.8-39.9 | μIU/ml |
| Urinary sodium | 30.25; 32.00; 34.35 | | mmol/l |
| 24-hour urinary sodium | 69,57; 85.86 | 150-250 | mmol/day |
| 24-hour urinary methylcatecholamines | 317 | < 1000 | μg |
| Urine osmolality | 260; 390; 130 | 50-1400 | mOsm/kg |
| 24-hour urine output | 2300; 2000; 2500 | | ml |
| Haemoglobin | 11.6; 12.4; 13.2 | 11.5-15.0 | g/dl |
| Haematocrit | 32.8; 33.1; 38.1 | 33.5-44.5 | % |
| TSH | 0.47 | 0.27 4.2 | |
| Ca 15.3 antigen | 23.7 | 0–20 | IU/ml |
| CEA | 3.9 | 0–3.4 | ng/ml |

*Selected sodium values are given in the text. Multiple determinations of potassium returned normal. Repeat measurements are separated by semi-colons, testing dates are available from the authors.*

abuse (zopiclone) for the past few years. Until 2009 he had led an active life. In the past 3 years the patient has quite irregularly been taking indapamide, an ACE inhibitor, a beta-blocker, a statin, amlodipine, aspirin, allopurinol and has periodically been taking non-steroid anti-inflammatory drugs.

In September 2009 the patient experienced several episodes of collapse accompanied by impaired consciousness, episodic convulsions, and low sodium (118 mmol/l; normal range: 135–147 mmol/l). The remaining laboratory results essential for the diagnosis are summarised in Table 1.

An abdominal ultrasound scan revealed a multiloculated cyst in the outer outline of the right kidney and numerous but haemodynamically insignificant atheromatous changes in the abdominal aorta and carotid arteries. The electrocardiogram and electroencephalogram were both normal. A head CT scan revealed multiple, disseminated, metachronic changes of vascular origin, cortical atrophy and leukoaraiosis. The 24-hour ambulatory ECG revealed a predominant sinus rhythm with isolated episodes of atrial fibrillation. Echocardiography revealed segmental contractility abnormalities and an ejection fraction (EF) of 54%. After the electrolyte imbalance had been corrected the patient was discharged and referred for further management in the outpatient setting. He was prescribed a beta-blocker, a statin, amlodipine, aspirin and oral electrolyte supplementation. This treatment failed to normalise the patient's blood pressure. In view of the considerable blood pressure surges, indapamide and an ACE inhibitor were restarted.

The patient was hospitalised again in October 2009 for another episode of hyponatremia (118 mmol/l), which this time was asymptomatic. Serum potassium was normal. An abdominal CT scan revealed, in addition to the previously described lesion in the right kidney (whose nature could not be established), a mass in the left adrenal gland consistent with an adenoma. Antihypertensive treatment was modified by discontinuing the diuretic. A subsequent hospitalisation was scheduled, aimed to repeat the assessment of the renal and adrenal lesions. After discharge, during the outpatient treatment, an attempt to restart indapamide was made due to considerable blood pressure surges, except this time, for fear of hyponatremia, the drug was initiated at a reduced dose of 1.5 mg q3d and with strict monitoring of serum electrolyte levels. Following two doses of indapamide sodium levels decreased from 130 mmol/l to 122 mmol/l. The drug was discontinued. Sodium levels after discontinuation of indapamide rose to 135 mmol/l.

The patient was hospitalised again in February 2010 in order to complete oncologic assessment. He underwent, among other investigations, an abdominal CT scan with the same findings as previously and

a chest CT scan revealing no neoplastic changes. No changes to the treatment were made and the diagnosis (indapamide-induced hyponatremia) was considered documented. In March 2010, in another follow-up examination, one month after discontinuation of indapamide, hyponatremia was detected yet again (128 mmol/l; N: 135-147 mmol/l). Given the necessity to verify the diagnosis a simultaneous determination of sodium levels in the serum and a 24-hour urine collection was made (132 mmol/l; N: 135-147 mmol/l, and 85.86 mmol/24 h (N: 150–250 mmol/24 h, respectively). Calculated serum osmolality was 273 mOsm/kg and ADH exceeded 30 ng/l (N: 2–6 ng/l).

## 3. Discussion

This case involves two clinical problems: hyponatremia and a difficult to treat hypertension. The left adrenal lesion may suggest a secondary nature of hypertension. However, the normal levels of 24-hour urinary methylcatecholamines, the normal cortisol levels (determined on several occasions) and the normal aldosterone level coupled with high renin and low sodium levels prompted us to treat the adrenal lesion as an incidentaloma. Hyponatremia on the other hand is the principal reason for reporting this case. Hyponatremia is most commonly divided into: acute (up to 48 hours) and chronic (more than 48 hours) according to the duration; hyperosmolar, normo-osmolar and hypo-osmolar according to plasma osmolality; and hypervolaemic, normovolaemic and hypovolaemic according to the degree of hydration. There are no laboratory tests that would provide the possibility to establish the duration of the electrolyte abnormality. The reported patient had been taking indapamide for many years, yet the clinical manifestations were fulminant (convulsions, loss of consciousness) and had not been preceded by any discernible prodromic phase or any event of any potential medical relevance. The patient's hyponatremia could therefore be classified as chronic, which subsequently for unknown reasons became uncompensated, or as acute. Plasma osmolality during the first hospitalisation was 278 mOsm/kg. During the subsequent hospitalisation plasma osmolality was not determined, but the 24-hour urinary output was 2300 ml, 24-hour sodium excretion was 69.57 mmol (N: 150–250 mmol/24 h) and urinary sodium was 32 mmol/l. The value of 30 mmol/l is a borderline value providing a laboratory confirmation of renal fluid loss [3]. Despite the reduced natriuresis, no clinical signs of fluid retention were observed at that time. The picture of near-normo-osmolar hyponatremia with normovolaemia, low natriuresis and relatively elevated urinary sodium may still be consistent with at least three disease entities: the syndrome of inappropriate antidiuretic hormone secretion (SIADH), cerebral salt-wasting syndrome (CSWS) and diuretic-induced hyponatremia.

The temporal relationship related to the administration and discontinuation of indapamide suggested the latter diagnosis. The two attempts to restart indapamide consistently resulted in hyponatremia. On the other hand, the many years' history of indapamide use was an argument against the diagnosis, as this condition is believed to develop within the first two weeks of treatment [3].

The diagnosis of SIADH, which may be secondary to many disease entities, was supported by the presence of normovolaemic, near-isotonic hyponatremia with a high urinary sodium in relation to plasma sodium, elevated NT-proBNP and the clinically high likelihood of cancer. The the many years of smoking and the unclear changes on ultrasound and CT scans prompted further investigation in this direction. SIADH is characterised by excessive ADH secretion in response to typical stimuli, which results in water retention in the body. A further consequence is the increased secretion of natriuretic peptides (such as BNP in our case), which consequently leads to natriuresis. The magnitude of this abnormality does not correlate with the severity of the process which initially caused it (dose of the drug, severity of cancer). The syndrome may be a complication of respiratory inflammation, but first of all of cancer, particularly small cell lung carcinoma. It may also accompany pancreatic and nasopharyngeal cancers and lymphomas, thymoma, pleural mesothelioma, inflammatory and vascular CNS disorders and may be a complication of treatment with dopamine agonists, carbamazepine, opiates, neuroleptic agents and other drugs [1,5,6]. The high plasma renin activity, however, is an argument against this diagnosis [7].

The diagnosis of CSWS was supported by the extensive neurological history and the head CT picture confirming numerous lesions of vascular origin [3].

Despite the well-documented causal relationship between the individual indapamide discontinuations and retreatment's, resulting in periods of hyponatremia and normal sodium levels, the case could raise a few doubts. According to the manufacturer's information, indapamide can cause hyponatremia, although many clinical studies emphasise its excellent tolerability [8-10]. Slow-release formulations in particular, and such were being used in the reported case, are considered safe [8,9]. With the exception of one report suggesting that indapamide-induced hyponatremia might be more frequent than commonly thought, the remaining

reports are anecdotal [13-16]. The abnormality is quite interesting, as the diuretic effect of the drug is very weak – too weak to cause any electrolyte imbalance, which has already been emphasised in the comments to reports of indapamide-induced hyponatremia [8]. In our case, in the last attempt one tablet of 1.5 mg q3d was given and a marked reduction in serum sodium was observed as early as following the second dose. The mechanism of indapamide-induced hyponatremia may therefore overlap with the pre-existing subclinical and undiagnosed SIADH. In the Medline database we failed to find any report of indapamide-induced hyponatremia in which ADH was determined. The diagnoses were made on the basis of dechallenge and rechallenge. We have also considered this test to be sufficient for establishing our diagnosis. It was not until we observed a different course of the illness from what we had expected that we were prompted to consider another aetiology.

## 4. Conclusions

The analysis of this case prompts one to determine ADH in patients with hyponatremia receiving indapamide. The apparently certain diagnosis of indapamide-induced hyponatremia may in fact be SIADH exacerbated by indapamide. This approach could allow for a negative verification of the hypothesis related to the possibility of hyponatremia being caused by indapamide.

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