

Cardiac arrhythmia triggered by diuretic-induced hyponatremia

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Abstract

Diuretics have a long and distinguished history in the treatment of hypertension and heart failure. Clinical practice guidelines recommend that diuretics should be considered to be as suitable as other antihypertensive agents for the initiation and maintenance of antihypertensive treatment. However, diuretics may potentially cause electrolyte disturbances and metabolic side effects. Diuretic-induced hyponatremia is probably more prevalent than generally acknowledged. We present an unusual case of indapamide-induced hyponatremia and hypokalemia complicated by cardiac arrhythmia. The adverse drug reaction was reversible and non-life-threatening, but this case serves as a reminder that careful evaluation and constant monitoring are necessary when prescribing diuretics.

Abstract

Diuretics are among the most important drugs in our therapeutic armamentarium for treating hypertension and heart failure. Clinical practice guidelines (CPGs) recommend that diuretics should be considered to be as suitable as other antihypertensive agents for the initiation and maintenance of antihypertensive treatment.¹ Diuretics are effective and economical and commonly prescribed by doctors in clinical practice. However, the setback is that diuretics may cause electrolyte disturbances and metabolic side effects. Severe diuretic-induced hyponatremia causes debilitating symptoms, such as confusion, falls and seizures, and can sometimes be fatal. Diuretic-induced hyponatremia necessitating hospital admission has been reported in retrospective studies. We present a patient with indapamide-induced hyponatremia and hypokalemia complicated by cardiac arrhythmia.

Case presentation

A 65-year-old Chinese male with hypertension had been on a combination antihypertensive drug (telmisartan-

amlodipine 40/5 mg once daily) for about three years. Due to inadequate blood pressure (BP) control, his general practitioner changed the antihypertensive treatment to a triple drug combination pill (perindopril-indapamide-amlodipine [5/1.25/5 mg]) in a once daily dose. Ten days after switching his antihypertensive agent to perindopril-indapamide-amlodipine, he presented to the Accident & Emergency (A&E) department for generalized weakness, dizziness, palpitations and vomiting. He did not complain of tinnitus or vertigo. There was no history of fall, injury or syncopal attack. He was a smoker, non-diabetic and did not consume alcohol. He denied taking any over-the-counter drug, herbal remedies or health supplements. On examination, he was afebrile and oriented but drowsy. His pulse was 86 beat/minute (irregular), and his BP was 150/90 mmHg. There was no pallor, cyanosis or pedal edema, and the jugular venous pressure was not raised. His chest was clinically clear, and the cardiac examination was unremarkable. A neurological examination showed no ataxia or focal neurological deficit. The electrocardiography (ECG) showed frequent premature atrial contractions (PACs). (Figure 1A).

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Figure (1A) ECG on admission. The non-sinus P wave in PACs occurs earlier than the expected sinus P wave and has a different morphology, such as notched, flattened, negative (retrograde), or may occur on the preceding T wave (hidden). In our case, a representative PAC is shown in the lead aVF (arrowhead), displaying 4 consecutive normal sinus P waves with normal QRS complexes, followed by a PAC with its P wave hidden in the preceding T wave. The PACs have narrow QRS complexes. The compensatory pause following the PACs resume exactly two P-P intervals after the last normal sinus beat (as illustrated in lead II) (1B) Normalization of ECG one week later. PACs, premature atrial contractions; P-P interval, time interval between two consecutive sinus P waves.

The serum Troponin T test (quantitative method) was negative. The chest X-ray showed mild cardiomegaly with a cardio-thoracic ratio of 60%. The blood investigations at admission revealed serum sodium of 115 mmol/L (hyponatremia) and potassium of 3.5 mmol/L (hypokalemia). The full blood count, liver function test, lipid profile, and thyroid hormone profile were normal (Table 1).

Table 1. Blood investigation on admission and follow-up

Blood investigation	On admission	On follow-up*	Normal limits
<i>Full blood count</i>			
Hemoglobin	15.2	-	13.0 – 17.0 g/dL
White cell count	9.2	-	4.0 – 11 x 10 ³ /μL
Platelets	314	-	150 – 400 x 10 ³ /μL

Blood investigation	On admission	On follow-up*	Normal limits
<i>Renal function test</i>			
Sodium	115	132	135 – 152 mmol/L
Potassium	3.5	4.7	3.6 – 5.4 mmol/L
Urea	3.1	3.5	2.3 – 6.8 mmol/L
Creatinine	66	69	60 – 130 µmol/L
Random blood glucose	8.3	-	4.0 – 7.8 mmol/L
<i>Liver function test</i>			
Alanine aminotransferase	33	-	5 – 55 IU
Aspartate aminotransferase	33	-	8 – 40 IU
<i>Lipid profile</i>			
Total cholesterol	5.4	-	<5.5 mmol/L
Triglycerides	1.09	-	0.40 – 1.54 mmol/L
HDL cholesterol	1.97	-	0.75 – 1.73 mmol/L
LDL cholesterol	2.9	-	< 3.4 mmol/L
<i>Thyroid function</i>			
FreeT4	21.4	-	10.0 – 28.2 pmol/L

*One week after discharge from an acute admission to the A&E department

The hyponatremia was treated by intravenous normal saline (0.9%) infusion. The patient was monitored as an inpatient in the A&E department for three hours. His symptoms improved after one pint of normal saline infusion. We recommended admission for further treatment and monitoring of cardiac arrhythmia. However, the patient discharged himself against advice. One week after discontinuation of perindopril-indapamide-amlodipine, the repeat serum sodium had increased to 132 mmol/L at follow-up. The serum potassium was corrected to 4.7 mmol/L. The patient was oriented, and his symptoms had resolved completely. The repeat ECG showed normal sinus rhythm (**Figure 1B**). The transthoracic echocardiography revealed an ejection fraction of 75 % with normal valves, normal wall motions and no visible mass or thrombus. Subsequently, the results of the 24-hour Holter monitor and exercise stress test were normal.

Discussion

We present a hypertensive patient presenting with indapamide-induced hyponatremia and hypokalemia complicated by cardiac arrhythmia. The patient did not have any known prior cardiac disease. After the cessation of the diuretic, the electrolyte imbalance was normalized, and the cardiac arrhythmia was no longer present. Kottwitz et

al. reported a case of hyponatremia associated with hydrochlorothiazide and amiloride in which the patient presented with a complete heart block.² Mouallem et al. described three patients with atrioventricular (AV) conduction defects, all of which occurred after episodes of severe hyponatremia. Diuretic-induced hyponatremia was observed in two patients. The findings suggest that hyponatremia may play a role in the pathogenesis of the observed AV conduction defects, but the association between cardiac conduction defects and hyponatremia is far from established.³ To our knowledge, PACs associated with hyponatremia has not been reported in the literature. PACs, also known as atrial premature complexes, are a common cardiac arrhythmia occurring both among healthy individuals and those with significant heart disease.

As the P wave in PACs originates outside of the sinoatrial (SA) node, the P wave morphology is different from the normal sinus P wave and occurs earlier than the expected sinus P wave. The non-sinus P wave in PACs can be notched, flattened, negative (retrograde), or may occur on the preceding T wave (hidden) if it is discharged very early. In PACs, the QRS complex is normal, whereas PVC has a wide QRS complex.

PACs have been considered a benign electrophysiological phenomenon that rarely

results in serious clinical consequences. The etiology of PACs include increased sympathetic activity as a result of pain or anxiety, atrial distention, atrial ischemia or infarction and pericarditis.⁴ PACs seldom require treatment beyond removal of the precipitating factor or treatment of the underlying disease.

However, Marcus et al. has described a PAC as a “wolf in sheep’s clothing.”⁵ This is because a high PACs burden may be a forerunner of atrial fibrillation/flutter, which is associated with a higher risk of stroke and death. In our patient, the PACs associated with diuretic-induced hyponatremia were non-life-threatening. It must be emphasized, however, that older or sicker patients with co-existing comorbidities may not tolerate hyponatremia. The CPGs recommend that diuretics should be considered to be suitable as beta-blockers, calcium-channel blockers, angiotension-converting-enzyme inhibitors and angiotensin receptor blockers for the initiation and maintenance of antihypertensive treatment.¹ The efficacy, safety and tolerability of diuretics have been evaluated in randomized-controlled trials. However, diuretic-induced hyponatremia is probably more prevalent than generally acknowledged. Severe diuretic-induced hyponatremia causes debilitating symptoms, such as confusion, falls and seizures, and can sometimes be fatal.⁶ Hyponatremia is one of the major adverse effects of thiazide and thiazide-like diuretics and is the leading cause of drug-induced hyponatremia requiring hospitalization. Indapamide is a non-thiazide diuretic, and its mechanism of action is similar to that of thiazide-diuretics. Between 1984 and 2000 in Australia, 84 cases of hyponatremia and 87 reports of hypokalemia, in which indapamide was the sole suspected drug, were submitted to the Adverse Drug Reactions Advisory Committee.⁷ Most cases involved elderly patients, and most reports involved an indapamide dose of 2.5 mg daily. In another retrospective study, eleven patients were admitted to a tertiary hospital between 2006 and 2009 with severe indapamide-related hyponatremia (defined as serum sodium < 125 mmol/L).⁸ All patients were female and elderly (age: 81.7 ± 5.8 years). A dose

of indapamide sustained-release 1.5 mg was taken daily by eight of the eleven patients. The other three patients took indapamide 2.5 mg in combination with perindopril. Increasing the use of diuretics will expose more patients to the risk of hyponatremia. Age-related changes in pharmacokinetics and pharmacodynamics make the elderly vulnerable to the development of adverse drug reactions. Drug-disease interactions or drug-drug interactions may occur because polypharmacy is more common in the older population. In patients on diuretics, especially the elderly, changes in conscious or mental states should prompt timely measurement of the serum sodium concentration. Diuretic-induced hyponatremia necessitating hospital admission is common enough to suggest that current monitoring regimens are suboptimal.⁹ Clinicians should be aware of the severe electrolyte disturbance arising from diuretics, and patients should be informed of the common manifestations of an adverse reaction.

Conclusion

Diuretic-induced hyponatremia is an important cause of preventable morbidity. Therefore, special attention should be given to its prevention. The adverse drug reaction in our case was non-life-threatening but serves as a reminder that careful evaluation and constant monitoring are necessary when prescribing diuretics.

Consent

Written informed consent was obtained from the patient for publication of this manuscript and the accompanying images.

Conflict of interest

The authors declare that there are no conflicts of interest.

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How does this paper make a difference to general practice?

1. Clinicians should be aware of the severe electrolyte disturbances which can arise from the use of diuretics.
2. Patients should be instructed about the common manifestations of adverse effects. A new onset of symptoms, such as lethargy, generalized weakness and dizziness, should prompt evaluation of the electrolyte profile.
3. In the elderly population, where polypharmacy and the presence of co-morbidities are common, there is increased vulnerability to diuretic-induced hyponatraemia.
4. When a diuretic is indicated, special attention should be given to the prevention of adverse side effects, and the patient should be monitored closely.
5. Concomitant use of a potassium supplement is indicated when hypokalemia is detected during the use of diuretics.

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