Severe thiazide-induced hyponatraemia during treatment with enalapril

Joseph G. Collier and David J. Webb

Department of Clinical Pharmacology, St George's Hospital Medical School, London SW17 ORE, UK.

Summary: A patient is described who developed mild hyponatraemia on two occasions when treated with bendrofluazide alone, but severe hyponatraemia when treated with the combination of enalapril and bendrofluazide.

Introduction

Severe hyponatraemia is a rare though well-recognized complication of treatment with thiazide diuretics, occurring particularly in elderly patients with hypertension, and more commonly in women.¹ We report here a case in which hyponatraemia induced by bendrofluazide was markedly enhanced by the concomitant use of the angiotensin converting enzyme (ACE) inhibitor enalapril.

Case report

The patient, a 68 year old retired Scottish woman, was referred for management of long-standing resistant hypertension. At the time of referral she had been taking atenolol (100 mg) and enalapril (20 mg) daily for 4 months and her blood pressure was 240/120 mm Hg supine and 245/125 mm Hg standing. Recent measurements of plasma sodium and potassium had been normal. In an attempt to reduce her blood pressure bendrofluazide 10 mg/day was added to her treatment, smaller doses given alone having been relatively ineffective prior to treatment with enalapril.

Three days after bendrofluazide was added the patient presented to the Accident and Emergency Department with a 24 hour history of weakness, headache, anorexia, nausea, irritability and tremor which are recognized symptoms of hyponatraemia; she had no history of polydipsia. Apart from a coarse tremor and supine blood pressure of 210/110 mm Hg clinical findings were unremarkable, with no evidence of extracellular fluid volume depletion or oedema. She was admitted to hospital and found to have a plasma

sodium of 115 mmol/l (normal range 135–145), potassium 3.3 mmol/l (3.6–4.6), bicarbonate 24 mmol/l (22–28), urea 7.2 mmol/l (2.5–8.4), creatinine 95 μ mol/l (50–110) and osmolality 246 mOsm/kg (280–300); simultaneous urine sodium was 57 mmol/l, potassium 81 mmol/l and osmolality 602 mOsm/kg. Measurements of plasma electrolytes were made by flame photometry. The patient's plasma was not lipaemic and had no paraprotein band.

Bendrofluazide and enalapril were stopped, and alternative antihypertensive therapy (initially methyl dopa; later verapamil) was added to the atenolol. Her daily water intake was restricted to 500 ml plus a volume matching her urine output. On days 1 to 5 of the admission, plasma sodium was 115, 119, 117, 124 and 128 mmol/l respectively. After 7 days on this regimen all of the biochemical parameters had returned to normal, and by two weeks free water tolerance was normal. Thyroid and liver function tests, response to synthetic ACTH, and plasma vasopressin were later shown to be normal. She was discharged taking atenolol and verapamil, and one week later enalapril was re-introduced.

Over the next 6 months she attended as an outpatient at weekly or fortnightly intervals. On each occasion her plasma urea and electrolytes were measured and all measurements of plasma sodium remained above 130 mmol/l. After 6 months enalapril was stopped when she developed a troublesome cough² and after a further month bendrofluazide 10 mg was restarted. On this occasion the treatment was tolerated for 2 weeks when she complained of nausea, diarrhoea and epigastric pain. The plasma sodium measured on the 14th day of bendrofluazide (10 mg/day) was 128 mmol/l. Later reintroduction of bendrofluazide (5mg/day) caused similar symptoms, and by the end of two weeks on this dose plasma sodium was again 128 mmol/l.

Correspondence: D.J. Webb, M.B., M.R.C.P.

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Discussion

ACE inhibitors have not been reported to cause hyponatraemia in hypertension, but may do so in heart failure.³ It is well recognized however that thiazides given alone may, rarely, cause a marked fall in plasma sodium in patients treated for hypertension, with the degree of hyponatraemia relatively reproducible on re-exposure.^{4,5} On taking bendrofluzide 10 mg alone for two weeks our patient developed only mild hyponatraemia (128 mmol/l). Accordingly the severe and sustained hyponatraemia (115 mmol/l) occurring within 3 days of starting the combination of enalapril and bendrofluzide is strong evidence of an interaction. Though we were not able to investigate its

mechanism, possibilities may include the alteration in renal haemodynamics, and the loss of the renin-mediated aldosterone response associated with the use of converting enzyme inhibitors.⁶ In our patient no impairment of renal, adrenal, or pituitary function was detected.

The combination of thiazide and ACE inhibitor is effective and widely prescribed both for hypertension and heart failure, and with this in view a fixed-dose combination preparation of captopril and hydrochlorothiazide (Ecazide) has recently been approved in France. Before such a preparation is marketed in the UK the risks of interaction between ACE inhibitor and thiazide diuretic will need particularly careful attention.

References

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