Fluconazole induced hyponatraemia

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TO THE EDITOR:

Hyponatraemia is frequently observed and usually caused by drugs. Fluconazole induced hyponatraemia remains under-reported.

An 82-year-old woman was admitted for rehabilitation. Past medical history was significant for hypertension, hypothyroidism, cervical stenosis and unilateral hydronephrosis. Drug history included lisinopril 5mg, levothyroxine 100mcg, amitriptyline 10mg and cefalexin 125mg. The patient was euvolaemic and examination was unremarkable. Routine haematology and biochemistry were normal.

During the first 24 hours the patient developed vomiting and dyspepsia. Body computerised tomography demonstrated unchanged hydronephrosis and no malignancy. She was empirically treated for urosepsis with intravenous co-amoxiclav and fluids. Within 24 hours serum sodium (Na) dropped from 134mmol/L

to 128mmol/L which was attributed to overhydration and vomiting. Oesophago-gastro-duodenoscopy on day 6 revealed gastritis and oesophageal candidiasis. On day 7 she was prescribed fluconazole 50mg and lansoprazole 30mg daily for 14 days.

Symptoms rapidly subsided, but Na continued to decline (Figure 1). Plasma glucose, lipids, protein, inflammatory markers and tests for thyroid, adrenal and renal function were found normal. Serum osmolality was 267mmol/L, urine osmolality 267mmol/L and urine Na 50mmol/L confirming syndrome of inappropriate anti-diuretic hormone secretion (SIADH) (Table 1).

Fluconazole was stopped and lansoprazole was substituted for famotidine (a histamine H2-receptor antagonist) on day 20 when Na was 121mmol/L, and daily fluid intake was restricted to 1L. Slow release salt tablets were also prescribed. 3 days after stopping both medications (on day 23) and with continued fluid restriction, Na dropped to 119mmol/L. Repeat serum osmolality was 257mOsmol/kg, urine osmolality 418mOsmol/kg and urine Na 33mmol/L confirming ongoing SIADH. Demeclocycline was prescribed on day 26 to counteract SIADH, and fluid intake was restricted to 750ml. This regimen was continued for 14 days.

7 days after cessation of fluconazole (on day 27), Na gradually increased. On day 38 (18 days after stopping fluconazole) Na was 127mmol/L and the patient remained well. Demeclocycline was stopped on day 40. On follow up, 5 weeks after stopping fluconazole, Na was 132mmol/L and the patient was asymptomatic.

Causes of hypotonic hyponatremia in a euvolemic patient include glucocorticoid deficiency, thyroid dysfunction, hyperlipidaemia (pseudo-hyponatraemia), SIADH or drugs. Our patient had been on long-term treatment with amitriptyline and lisinopril, and lansoprazole was replaced with famotidine early. Although proton pump inhibitors can cause hyponatraemia through SIADH, lansoprazole is the least likely agent to do so, and the effect is readily reversible on cessation of the culprit drug [1]; consequently, ongoing hyponatraemia cannot be credited to these medications. In light of biochemical analyses and elimination of other causes, the most likely cause of hyponatraemia in our patient was fluconazole induced SIADH. Arguably, lansoprazole may have contributed to the biochemical diagnosis of SIADH.

Fluconazole belongs to azole group of antifungals. After its approval in 1990, it soon became recognized as the more stable and less toxic azole antifungal when compared to ketoconazole and itraconazole. The half-life of fluconazole is 30 hours and it takes 6-10 days of daily dosing to reach a steady state in serum and around 11 days for its elimination from the body [2]. Lansoprazole, a proton pump inhibitor, has excellent and rapid absorption and reaches peak plasma levels in 1.7 hours. Although in older adults, clearance is decreased, the mean half-life remans between 1.9 and 2.9 hours [3]. Importantly, lansoprazole does not accumulate in the body and peak plasma levels remain unaltered by multiple dosing [4]. This makes it an unlikely culprit for ongoing hyponatremia. Causality assessment via Naranjo algorithm demonstrated probable adverse effect ($> 5/10$) in favour of fluconazole.

In vitro and preclinical in vivo studies have reported that fluconazole increases osmotic water transport in renal collecting ducts, thus corroborating an antidiuretic action [5]. This, alongside its pharmacokinetic data, supports the potential of fluconazole to precipitate a prolonged state of hyponatraemia. However, to date, no substantial clinical data are available to validate this proposed mechanism, and there are few reports suggesting a causal link between fluconazole and hyponatraemia. Our case is unique in that hyponatraemia was profound and protracted and likely attributable to fluconazole. Research to elucidate the role of fluconazole in the aetiology of hyponatraemia is awaited.

Legend Figure 1

Trend in serum Na. Day 0: intravenous fluids and antibiotics administered; Day 6: lansoprazole and fluconazole initiated; Day 17: 1L fluid restriction started; Day 20: lansoprazole and fluconazole stopped; Day 25: salt tablets prescribed; Day 26: 750ml fluid restriction; Day 27: demeclocycline started; Day 32: discharge; Day 38: 6 day follow up; Day 52: 20 day follow up

Legend Table 1

Serum and urinary biochemical analyses

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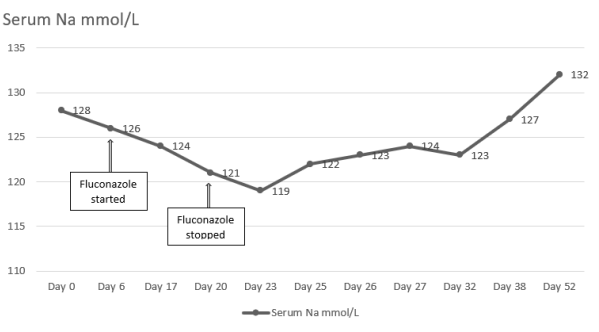

Day 6

Analysis	Result	Reference Value
Adjusted calcium (mmol/L)	2.38	2.20-2.60
Potassium (mmol/L)	4.4	3.5-5.3
Urea (mmol/L)	7.2	2.5-7.8
Creatinine (umol/L)	70	45-84
Estimated glomerular filtration rate (mLmin/1.73m^2)	70	>90
Thyroid stimulating hormone (mU/L)	0.70	0.27-4.2
Cortisol (nmol/L)	269	170-500
Alkaline phosphatase (IU/L)	109	35-104
Alanine aminotransferase (IU/L)	10	<34

Day 14

Analysis	Result	Reference Value
Serum osmolality (mOsmol/Kg)	267	275-295
Urine osmolality (mOsmol/Kg)	267	-
Urine Na (mmol/L)	50	>20
Serum glucose (mmol/L)	6.3	4.0-7.0
Triglycerides (mmol/L)	1.8	0 - 1.7
Total cholesterol (mmol/L)	5.1	1.21 - 5
Total protein (g/L)	71	60-80
Magnesium (mmol/L)	0.76	0.70-1.0
Phosphate (mmol/L)	0.89	0.81-1.45

Day 23

Analysis	Result	Reference Value
Serum osmolality (mOsmol/Kg)	257	275-295
Urine osmolality (mOsmol/Kg)	418	-
Urine Na (mmol/L)	33	>20