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[1] Haber, E, *et al*, *Journal of Clinical Endocrinology and Metabolism*, 1969, **29**, 1349.
[2] Ito, T, *et al*, *Journal of Clinical Endocrinology and Metabolism*, 1972, **34**, 106.
[3] Nicholls, M G, and Espiner, E A, *New Zealand Medical Journal*, 1975, **81**, 490.
[4] Nicholls, M G, *et al*, *Clinical Science and Molecular Medicine*, 1974, **47**, 301.
[5] Biglieri, E G, *et al*, *Journal of Clinical Endocrinology and Metabolism*, 1966, **26**, 553.

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Hyponatraemia: adverse effect of diuretic treatment

Hyponatraemia occurring in cardiac failure and exacerbated by diuretics is well known.[1] Intractable oedema, azotaemia, and increased total exchangeable sodium are characteristic[2] of the condition and the prognosis is poor. Hyponatraemia with sodium depletion is a rare consequence of diuretic treatment.[1 2] Four patients taking diuretics presented with symptoms of hyponatraemia without cardiac failure. Administration of sodium produced rapid and sustained improvement.

Case histories

Four patients were admitted to hospital with histories of deteriorating health over the previous weeks or months. All had been receiving daily diuretic treatment (see table). None was in cardiac failure and peripheral oedema was absent or minimal. Subconjunctival oedema was noticed in three. Physical signs of saline depletion were absent. Biochemical analysis showed hyponatraemia and normal blood urea concentrations. There were no endocrine or renal abnormalities likely to cause hyponatraemia. They were treated with intravenous saline infusion with added potassium followed by oral supplements until plasma electrolyte balance returned to normal. Dosage of intravenous and oral sodium ranged from 804 to 1506 mmol, and of potassium 60 to 420 mmol. Complete and sustained recovery accompanied the correction of plasma electrolyte imbalance and withdrawal of diuretics. Follow-up ranged from three months to three years.

Discussion

The absence of signs of cardiac failure or peripheral oedema together with the rapid and sustained improvement in the patients' condition after sodium administration suggests that hyponatraemia had occurred in the presence of a sodium deficit. Diuretic treatment was the most likely cause, although in one diabetic patient chlorpropamide may also have contributed.[3]

It is important to distinguish hyponatraemia with sodium deficit from the more common dilutional hyponatraemia of cardiac failure because administration of sodium in the latter condition may be deleterious.[4] The clinical features of our four patients characterise the syndrome. Symptoms are those of hyponatraemia—lethargy, weakness, slowing of cerebration, anorexia, and nausea, progressing to coma and convulsions.[4] Examination usually shows normal hydration with no peripheral oedema, although subconjunctival oedema may be seen. Plasma sodium and chloride concentrations are low, while blood urea concentrations are normal.

Dilutional hyponatraemia in cardiac failure results from depressed free water production. Several mechanisms have been implicated,[1] some of which may also produce hyponatraemia with sodium deficiency. Natriuresis and extracellular fluid volume depletion after diuretics usually stimulate increased proximal tubular reabsorption of sodium and increased aldosterone secretion. These homoeostatic mechanisms decrease further natriuresis, and sodium output returns to pretreatment levels.[5] Patients who become sodium deficient may suffer a partial failure of these mechanisms. The elderly would thus be more susceptible.

Hyponatraemia implies dilution in the extracellular compartment. The ability of the kidney to excrete dilute urine depends on adequate delivery of sodium to the distal part of the ascending limb of the loop of Henle and is therefore decreased in sodium depletion.[4] Furthermore, diuretics prevent reabsorption of sodium ions in that part of the nephron and characteristically decrease free water production.[1] The thiazide diuretics are particularly implicated.[3] They have a potent effect in the diluting segment of the nephron, and being long-acting allow little time for homoeostatic mechanisms to operate. High levels of antidiuretic hormone have also been reported in diuretic-induced hyponatraemia.[3] Thus a combination of altered physiological response and the specific pharmacology of the diuretics explains the loss of sodium and chloride ions and concomitant retention of water.

Hyponatraemia with sodium deficit after diuretic treatment may be easily missed if plasma electrolyte concentrations are not measured in elderly patients taking diuretics who complain of a general deterioration in health.

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[1] Davies, D L, and Wilson, G M, *Drugs*, 1975, **9**, 178.
[2] Edelman, I S, *Metabolism*, 1956, **5**, 500.
[3] Fichman, M P, *et al*, *Annals of Internal Medicine*, 1971, **75**, 853.
[4] Leaf, A, *New England Journal of Medicine*, 1962, **267**, 24, 77.
[5] Nicholls, M G, *et al*, *Clinical Science and Molecular Medicine*, 1974, **47**, 301.

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Clinical and biochemical features and treatment in the four cases

Age (years) and sex	Clinical features				Plasma biochemistry (mmol/l)					Drugs and daily dose
	Anorexia, nausea, and vomiting	Slowed cerebration, lethargy, and weakness	Convulsions	Subconjunctival oedema	Urea	Na^+	K^+	Cl^-	HCO_3^-	
80 F	+ + +	+		+	6·7	107	3·6	71	23	Cyclopenthiazide 0·75 mg; potassium chloride 1·8 g; digoxin 0·25 mg
71 F		+ + +	+		5·0	<110	4·1	80	16	Frusemide 40 mg; potassium chloride 1·8 g; digoxin 0·25 mg; imipramine 75 mg
49 F		+ + +		+	5·0	115	3·2	78	25	Bendrofluazide 5 mg; potassium chloride 1·2 g; chlorpropamide 500 mg; phenformin 25 mg; methyldopa 1 g
84 F	+ + +	+ + +		+	3·2	105	3·6	70	24	Amiloride 5 mg; hydrochlorothiazide 50 mg

Conversion: SI to traditional units—Plasma urea: 1 mmol/l ≈ 6 mg/100 ml. Plasma electrolytes: 1 mmol/l = 1 mEq/l.