Comment

Good results from splenectomy have been reported in 11 out of 13 patients who showed a spleen:liver ratio >2·3 at $t_{\frac{1}{2}}^{51}Cr$,[1] and from another series of 10 there were three similar patients.[3] In the latter series the remaining seven patients all had low spleen:liver ratios (<2·3), four responded to splenectomy, and three failed. Like others,[2] we have confirmed that patients with low spleen:liver ratios (<2·5 at $t_{\frac{1}{2}}^{51}Cr$) can respond well to splenectomy. As well as the three patients with low ratios who did well, we found two out of five patients with high ratios who did badly after surgery.

When characterised, IgG was found to have sensitised the erythrocytes of patients responding to splenectomy, while complement alone was found in patients who did badly. This accords with recent findings that IgG-coated cells are sequestered predominantly in the spleen. With complement-sensitisation organ sequestration patterns were found to be normal.[5]

In this small group of patients the data confirm that surface-counting measurements using ^{51}Cr-labelled red cells are not reliable indicators of the outcome of splenectomy.

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[1] Goldberg, A, Hutchison, H E, and Macdonald, E, *Lancet*, 1966, **1**, 109.
[2] Ahuja, S, Lewis, S M, and Szur, L, *Journal of Clinical Pathology*, 1972, **25**, 467.
[3] Allgood, J W, and Chaplin, H, jun, *American Journal of Medicine*, 1967, **43**, 254.
[4] Jandl, J H, *et al*, *Journal of Clinical Investigation*, 1956, **35**, 842.
[5] Borne, A E, *et al*, *Clinical and Experimental Immunology*, 1973, **13**, 561.

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Liquorice toxicity and the renin-angiotensin-aldosterone axis in man

We studied the electrolyte status and renin-angiotensin-aldosterone axis after the withdrawal of liquorice in four ill women aged 38 to 55 years admitted with chronic liquorice intoxication. They had consumed 25-200 g liquorice daily for six months to five years.

Methods and results

Plasma renin activity (PRA), plasma aldosterone, plasma angiotensin II, and urinary aldosterone were measured, using standard radioimmunoassay techniques,[1-4] in these four patients on four occasions: (*a*) when they were first admitted and receiving a normal hospital diet, (*b*) on the fifth day of metabolic balance (sodium 10 mmol (mEq)/day; potassium 100 mmol (mEq)/day), (*c*) on the last day of balance, and (*d*) at two to four months' follow-up, on a normal home diet.

On a normal hospital diet urinary potassium excretion exceeded 40 mmol/24 hours in all four patients in the face of plasma potassium values of 1·6-2 mmol/l. On the fixed 10-mmol/day low-salt diet sodium balance was negative. The total urinary deficit ranged from 419 mmol over six days in one patient to 613 mmol over 11 days in another. In contrast, potassium balance was positive (423 mmol to 441 mmol over 6 to 11 days), and by the sixth day of low-salt diet plasma potassium had returned to normal in each case. In three patients plasma potassium rose above normal (5·3, 5·4, and 5·7 mmol/l) on days 10, 11, and 12, respectively, and potassium supplements had to be stopped. Plasma electrolytes remained normal thereafter, both during hospital admission and at follow-up two to four months later. Intravenous salt loading did not lead to excessive potassium excretion in any patient.

Renin, angiotensin, and aldosterone values during metabolic balance are summarised in the table. On the normal hospital diet all four patients had subnormal urinary aldosterone levels and PRA. These subnormal levels continued despite the low salt challenge of up to 12 days. Plasma aldosterone and plasma angiotensin II levels, while relatively normal under basal conditions, were abnormally low during low salt challenge.

Assessment of renin-angiotensin-aldosterone axis on four days in four patients withdrawn from liquorice. Patients were supine when 8-am values were measured and standing when 10-am values were measured

Case No:	1	2	3	4	Normal range (10-am standing)
On admission (normal diet)					
Urinary aldosterone (nmol/24 h)	2·8	8·3	2·8	4·0	8·3-50
Plasma aldosterone (pmol/l): 8 am	111	139	83	306	
10 am		278	111		139-556
PRA (nmol/l/h): 8 am	0·26	0	0·11	0·09	0·15-1·54
10 am		0·17	0·43		0·38-2·69
Plasma angiotensin (pmol/l): 8 am		28·5	28·5	38	
10 am		35·2	28·5		19-66·5
5th day of low-salt diet					
Urinary aldosterone (nmol/24 h)	5·5	22·2	2·8	6·0	41·6-221·6
Plasma aldosterone (pmol/l): 8 am	167	139	195		
10 am	195	445	167	390	445-2224
PRA (nmol/l/h): 8 am	0·04	0·45	0·25		
10 am	0·23	2·07	0·26	0·25	3·85-30·8
Plasma angiotensin (pmol/l): 8 am	26·6	38	23·8		
10 am	28·5	47·5	26·6	46·6	76-200
Last day of salt depletion					
	(Day 12)	(Day 7)	(Day 11)	(Day 11)	
Urinary aldosterone (nmol/24 h)	11·1	12·5	11·1	8·0	
Plasma aldosterone (pmol/l): 8 am	167	222	167	445	
PRA (nmol/l/h): 10 am	1·94			3·2	
Follow-up					
Urinary aldosterone (nmol/24 h)	24·9	36	30·5	8·3	
Plasma aldosterone (pmol/l): 10 am	361	334	189	360	
PRA (nmol/l/h): 10 am	2·45	0·77	0·75	0·67	
Plasma angiotensin (pmol/l): 10 am	52·3	29·0	35	35	

Conversion: SI to traditional units—Urinary aldosterone: 1 nmol/24 h ≈ 361 ng/24h. Plasma aldosterone: 1 pmol/l ≈ 0·036 ng/100 ml. PRA: 1 nmol/l/h ≈ 1·3 ng/ml/h. Plasma angiotensin II: 1 pmol/l ≈ 1·05 pg/ml.

Comment

The clinical features in all cases were similar to those described in previous cases of severe liquorice intoxication. In the first two to three days after the withdrawal of liquorice inappropriately excessive amounts of potassium were excreted in the face of subnormal plasma potassium levels. This hallmark of mineralocorticoid excess was presumably due to the continued action of the glycyrrhizinic acid component of liquorice on renal tubular potassium secretion. After this came a phase of sodium loss and potassium retention. This inversion of the urinary sodium: potassium ratio during salt deprivation was in strong contrast to the sodium and potassium retention normally seen in patients with Conn's syndrome. Indeed, this inversion will distinguish liquorice intoxication from primary aldosteronism without PRA, aldosterone, or angiotensin II having to be measured. Presumably the natriuresis and potassium retention are related to the effects of extracellular volume expansion and paralysis of the renin-angiotensin-aldosterone system similar to that observed in patients with primary aldosteronism after removal of an aldosterone-secreting tumour. The electrolyte response to intravenous salt loading was normal, thereby excluding an endogenous source of mineralocorticoid other than aldosterone. The normal follow-up electrolyte and renin-angiotensin-aldosterone axis assessment also supported this conclusion in all cases.

Subnormal urinary and plasma aldosterone levels and PRA clearly indicated suppression of the renin-angiotensin-aldosterone axis in all patients. Furthermore, these hormones and plasma angiotensin II gave a blunted response to five days of low-salt challenge. Subnormal angiotensin levels were noted only after salt deprivation and were therefore less discriminatory than PRA under normal basal conditions. In one patient the renin-angiotensin-aldosterone axis remained suppressed for at least 14 days after the withdrawal of liquorice, despite 12 days of salt restriction. This paralysis of the axis led to mineralocorticoid deficiency, as shown by raised serum potassium levels after continued salt restriction in three of the four patients. All patients showed normal values two to four months later, however, indicating that long-term suppression of the renin-angiotensin-aldosterone axis is uncommon despite several years of liquorice ingestion. This finding is in contrast to the prolonged suppression observed after the removal of some aldosterone-secreting tumours.[5]

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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.