Hyperkalaemia in diabetes mellitus—potential hazards of coexisting hyporeninaemic hypoaldosteronism

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Summary

Two patients with insulin-dependent diabetes mellitus (Type I), developed severe, life-threatening hyperkalaemia, the first following treatment with spironolactone, the second during treatment for staphylococcal septicaemia when glucose-induced hyperkalaemia occurred. Investigations demonstrated co-existing hyporeninaemic hypoaldosteronism. Prompt recognition of this combined hormone-deficiency syndrome led to appropriate treatment and recovery. The biochemical features and clinical importance of hyporeninaemic hypoaldosteronism are discussed.

KEY WORDS: vasculitis, autonomic, neuropathy.

Introduction

Normal levels of serum potassium are maintained through the interplay between intake, renal potassium excretion, mineralocorticoid function and transcellular potassium transport regulation, in which insulin and glucose play an important role (Goldfarb *et al.*, 1975; Cox, Sterns and Singer, 1978).

Combined deficiencies of both insulin and aldosterone may therefore be associated with predisposition to hyperkalaemia, which may be life-threatening (Goldfarb *et al.*, 1976).

We describe here two diabetic patients in whom severe hyperkalaemia occurred in common clinical situations as a consequence of coexisting insulin deficiency and hyporeninaemic hypoaldosteronism.

Case 1

A 52-year-old housewife developed Type I (insulin-dependent) diabetes mellitus following subtotal pancreatectomy for chronic relapsing pancreatitis in

1957. Diabetic control was maintained with total daily insulin doses of 30–48 units. In September 1981 she developed bilateral ankle oedema and a painful nodular vasculitis of uncertain aetiology. Spironolactone 100 mg/day was prescribed and 4 weeks later the serum potassium was recorded at 7.2 mmol/l and 8.4 mmol/l. She was admitted to hospital and treated with glucose, insulin and potassium exchange resins. The spironolactone was discontinued. Further investigations were performed on a Metabolic Unit when it became apparent that hyperkalaemia (serum potassium greater than 5.0 mmol/l) had been present intermittently since 1970 (Fig. 1). The results of investigations on admission to the Metabolic Unit showed serum sodium 137 mmol/l, potassium 5.8 mmol/l, urea 9.7 mmol/l, creatinine clearance 42 ml/min, 24-hr urinary potassium 30 mmol, capillary pH 7.24 P_{CO_2} 4.6 kPa (34.5 mmHg), bicarbonate 14 mmol/l, base excess—12 mmol/l, blood glucose 14 mmol/l. There was intermittent glycosuria but no ketonuria. Results of circulating plasma renin activity (PRA) and aldosterone measured recumbent after 2 hr ambulant, and after intravenous frusemide are shown in Table 1. Low concentrations of PRA and aldosterone were found and there was no increase after standing or following frusemide, confirming the diagnosis of hyporeninaemic hypoaldosteronism. There was a normal cortisol response following synacthen 250 µg intramuscularly (basal cortisol 415 nmol/l; 30 min 785 nmol/l). A review of previous admissions when diabetic ketoacidosis had been reported showed that although systemic acidosis had been frequently documented ketonuria was never found.

Treatment with 9- α -fludrocortisone, 0.2 mg daily, was commenced. Within 48 hr the serum potassium had fallen below 5.0 mmol/l and remained normal subsequently. Acid-base status returned to normal at the same time.

FIG. 1. Simultaneous levels of serum potassium and blood glucose in Case 1 from 1970 to 1982, and the response to fludrocortisone.

TABLE 1. Plasma renin activity (PRA) and plasma aldosterone levels recumbent, ambulant and after frusemide challenge in Cases 1 and 2. Samples were measured in different assay systems as indicated by the normal ranges. In Case 2, a dose of 40 mg frusemide was used (in view of moderate renal failure) and this produced a brisk diuresis

	PRA (ng/ml/hr)	Normal range (ng/ml/hr)	Aldosterone (pmol/l)	Normal range (ng/ml/hr)
<i>Case 1</i>				
Recumbent	0.110	(0.3-1.20)	130	(135-400)
Ambulant	0.146	(0.6-2.00)	170	(270-830)
After frusemide 20 mg i.v.				
- 30 min	0.074		135	
0 min	0.071		105	
+ 15 min	0.097		80	
+ 30 min	0.064		118	
+ 45 min	0.083		103	
+ 60 min	0.029		155	
<i>Case 2</i>				
Recumbent	1.6	(1.7-4.5)	130	(100-500)
Ambulant	1.9	(3.0-8.0)	160	(expected range) (200-1000)
After frusemide 40 mg i.v.				
- 30 min	1.8		80	
0 min	1.8		100	
+ 15 min	1.9		50	
+ 30 min	2.1		70	
+ 45 min	1.0		—	
+ 60 min	1.0		40	

Case 2

A 39-year-old male developed Type I (insulin-dependent) diabetes at the age of 8 years. He was registered blind due to diabetic retinopathy in 1979 and showed evidence of diabetic nephropathy (creatinine clearance 15 ml/min), sensory and autonomic neuropathy and hypertension. He experienced gusta-

tory and nocturnal sweating regularly. During August 1982 he developed a staphylococcal septicaemia and an acute prostatic abscess. He was given appropriate antibiotic therapy. Control of the diabetes was difficult to achieve because of the combination of severe systemic infection, renal insufficiency and recurrent vomiting related to intermittent gastric

atony. However ketoacidosis did not occur at any stage of his illness. During a 2-week period beginning in late September 1982, hyperglycaemia and hyperkalaemia developed, simultaneous levels of which were significantly correlated ($r=0.81$; $P=0.01$). There was no significant correlation between levels of blood glucose and potassium at any other time.

When he had recovered from the septicaemia, investigations confirmed the diagnosis of hyporeninaemic hypoaldosteronism as in case 1 (Table 1). There was a normal cortisol response following 250 μ g synacthen intramuscularly (basal 380 nmol/l; 30 mins 730 nmol/l). 24-hr urine potassium 36 mmol. A mild metabolic acidosis was noted pH 7.30 P_{CO_2} 5.2 kPa (39.0 mmHg), bicarbonate 18.0 mmol/l, base excess -7.0 mmol/l. Gustatory and nocturnal sweating occurred, at times simulating hypoglycaemic attacks. House-staff were reminded not to administer intravenous dextrose in such circumstances, without first measuring the blood glucose concentration, in case dangerous hyperkalaemia should be precipitated. The patient later developed salt and water retention, treated with a combination of diuretics (frusemide 80 mg and bendrofluazide 10 mg daily). The serum potassium concentration became normal and has remained so. The acid-base status was corrected simultaneously. Overall renal function did not change significantly during or following his acute illness (serum creatinine 372 ± 36.2 s.d. μ mol/l—mean of 20 samples).

Discussion

In adult patients, the isolated deficiency in aldosterone secretion is a consequence of impaired or absent renal secretion of renin. This syndrome is known as hyporeninaemic hypoaldosteronism (Schambelan, Stockigt and Biglieri, 1972). Adrenal glucocorticoid production is normal.

Since aldosterone is required to augment renal excretion of potassium and hydrogen ions, this disorder results in hyperkalaemia, and metabolic acidosis, to which impaired renal ammonia production in the presence of hyperkalaemia also contributes (Szyzlan *et al.*, 1976).

Diabetes mellitus is a recognized associated disorder, but hyporeninaemic hypoaldosteronism has also been observed with interstitial nephritis, gout, lead nephropathy, hypercalcaemia (Schambelan, Sebastian and Hulter, 1978) and some cases of drug toxicity in which juxtaglomerular prostaglandin production may be impaired. In diabetes, reduced renin secretion may be due to small vessel disease in the kidney, autonomic neuropathy or the production of an inactive form of renin ('big renin'), which has been detected in the circulation of some diabetic patients (DeLeiva *et al.*, 1976). Coexisting renal

disease is probably required to allow full expression of aldosterone deficiency. However, the degree of renal failure has not been sufficient in itself to explain the hyperkalaemia. This syndrome may account for 10% of all cases of hyperkalaemia and 50% of cases of apparently unexplained hyperkalaemia (Tan and Burton, 1981), but it is rarely recognized in clinical practice.

Insulin also has an important role in potassium homeostasis by increasing in response to potassium administration and by promoting cellular uptake of potassium (Santeusano *et al.*, 1973). Furthermore, hyperglycaemia induces an osmotic redistribution of potassium from intracellular to extracellular fluid (Goldfarb *et al.*, 1975), so that insulin deficiency may contribute to the development of hyperkalaemia, particularly when there is a coexisting deficiency of aldosterone.

In Case 1, treatment with the aldosterone antagonist spironolactone further impaired renal potassium excretion, and severe hyperkalaemia developed during a period of relative insulin deficiency and hyperglycaemia. Intermittent hyperkalaemia had been observed in this patient since 1970, implying that hypoaldosteronism might have been present since then, but only became apparent when spironolactone was prescribed. We have not found previous reports of this. Hospital admissions with hyperglycaemia and 'ketoacidosis' without ketonuria being recorded represented the metabolic acidosis of hypoaldosteronism, and acid-base status returned to normal as soon as potassium levels fell with fluidro cortisone therapy.

In Case 2, insulin and aldosterone deficiency combined to produce severe hyperkalaemia when diabetic control deteriorated and hyperglycaemia developed. This is analogous to the hyperkalaemia which develops in patients with combined insulin and aldosterone deficiency when they are given intravenous glucose loads (Goldfarb *et al.*, 1975; Goldfarb *et al.*, 1976). Under these circumstances, therefore, the administration of hypertonic glucose for alleged hypoglycaemia, might have provoked potentially dangerous hyperkalaemia. Renal failure probably contributed less to the potassium rise in this subject than the metabolic acidosis and hyperglycaemia, since hyperkalaemia is infrequent in patients with non-oliguric stable chronic renal failure because of tubular secretion of potassium (Leaf and Camara, 1949). Furthermore, treatment with frusemide and bendrofluazide corrected the hyperkalaemia and the metabolic acidosis simultaneously, whilst overall renal function did not change. Frusemide is known to produce a kaliuresis and increased net acid excretion and to correct the metabolic acidosis in such patients (Sebastian and Schambelan, 1977). Fludrocortisone was not given to this patient because salt and water

retention developed. Type II (non-insulin-dependent) diabetes may also be associated with glucose-induced hyperkalaemia (Rosenstock *et al.*, 1982), but the clinical significance of this, if any, remains unclear. The presence of hyperkalaemia in diabetics without ketosis and who are not in advanced renal failure should raise the suspicion of hyporeninaemic hypoaldosteronism. Such subjects are uniquely sensitive to aldosterone antagonists which may provoke severe hyperkalaemia. Mild metabolic acidosis which persists in the absence of ketosis should arouse similar suspicions. Furthermore, sweating attacks simulating hypoglycaemia occurring in diabetics with autonomic neuropathy and/or systemic infection, should not be treated with hypertonic glucose, without confirmation of hypoglycaemia in case potentially hazardous hyperkalaemia should result. Sudden deaths from hyperkalaemia might be erroneously attributed to ischaemic heart disease or hypoglycaemia. In a recent survey by Tunbridge of 453 deaths in diabetics under the age of 50 years, 59 were assumed to result from ischaemic heart disease, and nine from hypoglycaemia (Tunbridge, 1981).

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