Death following non-ketotic hyperglycaemic coma during diazoxide therapy and peritoneal dialysis

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DIAZOXIDE is considered an effective and safe drug in the treatment of hypertension (Pohl and Thurston, 1971). Its hyperglycaemic effect is well known but this is rarely a serious hazard. Two recent reports have described non-ketotic hyperglycaemic coma complicating therapy with both the oral (Harrison, Rutter and Taylor, 1972) and intravenous (Charles and Danforth, 1971) form of the drug. The purpose of this report of a third case, which is the first to end fatally, is to re-emphasize this hazard and to discuss some of the factors which may have contributed to such severe hyperglycaemia in this instance.

Case report

A 44-year-old West Indian negro was admitted to The London Hospital in November 1971, with a 3 month history of dyspnoea and nocturia. There was no history of diabetes or renal disease, nor was there a family history of the former condition, but one brother did have hypertension. On examination there were signs of congestive cardiac failure, a blood pressure of 260/175 and grade three hypertensive retinopathy. The urine contained large quantities of albumin, numerous hyaline casts and a few red blood cells. Chest radiography showed cardiomegaly and pulmonary congestion and the electrocardiogram demonstrated left ventricular hypertrophy and widespread T wave inversion. Plasma electrolytes were normal but the blood urea was 147 mg/100 ml and the creatinine clearance was 18 ml/min. The intravenous pyelogram, 24 hr urinary vinyl mandelic acid excretion, anti-streptolysin O titre and autoantibody screen were normal. His hypertension was controlled initially with intramuscular guanethidine and subsequently with oral bethanidine and frusemide. At the time of discharge, three weeks later, the diastolic blood pressure was 110 mm Hg and there was no significant change in blood urea concentration.

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He returned to the West Indies at this time and on return 2 months later, having not kept to his drug regime, his blood pressure had risen to 260/170 mm Hg and the blood urea was 263 mg/100 ml. Control of the hypertension with sodium restriction, diuretics, guanethidine and bethanidine was unsuccessful. A change of therapy to diazoxide 400 mg oral daily, and intravenous boluses of 300-600 mg, together with frusemide over the next 6 days also failed to give a persistently reduced blood pressure. A random blood glucose prior to treatment with diazoxide was 110 mg/100 ml. It was considered this resistance was due to sodium retention and therefore peritoneal dialysis was instituted using hourly cycles of Dialaflex No. 63 (sodium 130.5 mOsm, Dextrose 75.5 mOsm) and No. 62 (sodium 140.9 mOsm, Dextrose 353.3 mOsm) in a ratio of 3:1. No further oral diazoxide was given but 2100 mg of this drug was required intravenously during the first 2 days of dialysis to keep the blood pressure between 190/90 and 200/110 mm Hg. This made a total of 3600 mg of intravenous diazoxide and 2400 mg of the oral form which had been given in an 8 day period. At the end of these 2 days dialysis the blood urea was 159 mg/100 ml, the plasma electrolytes were normal and the blood glucose was 168 mg/100 ml. During these 48 hr his temperature rose to 101°F due to a respiratory tract infection, which was treated with Ampicillin and Cloxacillin, and the urinary output fell, although an average of 1 l/day was maintained with the continued use of 120 mg of frusemide daily.

Despite these measures, however, the patient's level of consciousness, which had deteriorated steadily throughout this admission continued to worsen. Daily urine testing for glycosuria had been consistently negative but during the third day of dialysis heavy glycosuria suddenly occurred and the blood glucose was found to have risen to 822 mg/100 ml from 168 mg/100 ml 48 hr previously. The urine contained no ketones and the plasma electro-

lytes were normal. Peritoneal dialysis was stopped and the hyperglycaemia was treated with insulin and hypotonic fluids. The blood glucose was reduced to 500 mg/100 ml over the next 12 hr but he now sustained a brainstem infarction and he died a few hours later.

Post mortem examination confirmed the presence of infarctions in the pons and both cerebral hemispheres. There was severe atheroma of the basal arteries of the brain. The kidneys were normal weight and size. Microscopy showed changes consistent with treated malignant hypertension and there was no evidence of glomerulonephritis. The pancreatic islets were normal.

Discussion

In the currently reported case, as in the other two cases of non-ketotic hyperglycaemia coma (Harrison *et al.*, 1972; Charles and Danforth, 1971), there was significant impairment of renal function. It seems likely, therefore, that the decreased carbohydrate tolerance which occurs in uraemia either because of increased peripheral resistance to insulin (Horton, Johnson and Lebovitz, 1968; Cerletty and Engbring, 1967) or decreased insulin levels (Hampers *et al.*, 1966; Horton *et al.*, 1968) played a part in the hyperglycaemia of these patients. Despite this impairment of carbohydrate tolerance in uraemia, hyperglycaemic coma in non-diabetic uraemic patients is very rare and has, in fact, only been described in patients not receiving hyperglycaemic drugs, during peritoneal (Boyer, Gill and Epstein, 1967) and haemodialysis (Potter, 1966). It is known that large quantities of glucose may be absorbed from dialysate fluids (Boen, 1961) and it seems reasonable to suppose this, together with uraemia *per se*, were factors in our patient's hyperglycaemia.

Diazoxide is known to inhibit pancreatic secretion of insulin (Steinke and Soeldner, 1968) and peripheral glucose metabolism (Tabachnick and Gulbenkian, 1968), and mild degrees of hyperglycaemia during therapy are well recognized (Pohl and Thurston, 1971). On the other hand, non-ketotic hyperglycaemic coma has been described on only two previous occasions (Harrison *et al.*, 1972; Charles and Danforth, 1971), and ketoacidosis in only a single case (Updike and Harrington, 1969). Why such a severe degree of hyperglycaemia occurred in our patient, and did so with such rapidity as in Charles' patient, is not known. The pyrexia which developed in our patient may be implicated by causing an increased release of diazoxide from its protein binding sites, as it is known that noncovalent binding is decreased by increasing temperature (Sellers and Kock-Wesser, 1969). It is also perhaps possible that the frusemide, which was used concurrently, caused some degree of hyperglycaemia

either directly or by competing with diazoxide for binding sites. Charles implicated reduced renal clearance of diazoxide in his case, but although our patient also had a reduced urine output, there is no reason to suppose that unbound diazoxide would not be cleared by peritoneal dialysis.

Our patient almost certainly died due to brainstem infarction. It seems likely that hyperglycaemia played a part in this as thrombosis and infarction are known complications of hyperosmolar states (Hockaday and Alberti, 1972). There appears to be an increased incidence of non-ketotic hyperosmolar coma in West Indian negroes (Pyke, 1970) and it has been suggested that sickle cell trait may predispose to arterial thrombosis in such cases (Hockaday and Alberti, 1972). Haemoglobin electrophoresis on our patient was, however, normal.

In conclusion, it should be stressed that although diazoxide is usually a safe drug, hyperglycaemic coma of rapid onset does occur, albeit rarely. It is suggested that uraemia, pyrexia, infection, concurrent drug therapy and peritoneal dialysis may increase the chances of this hazard.

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The treatment of malignant ventricular tachycardia by aorto-coronary saphenous vein bypass graft

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Summary

A 61-year-old man with a previous cardiac infarction had at least fifteen attacks of ventricular tachycardia which finally did not respond to either drug or electrical therapy. Angiography showed a blocked right coronary artery and a non-contractile portion of postero-inferior left ventricular wall.

An aorto to right coronary saphenous vein bypass graft was inserted, and although attacks of tachycardia occurred following the operation these were of short duration and reverted spontaneously.

He has been free of tachycardia for 5 weeks, with a greatly improved effort tolerance.

Introduction

Ventricular tachycardia invariably leads to a severe deterioration of cardiac function in patients with heart disease. The wide range of electrical and pharmacological remedies currently available has greatly improved the outlook in what was formerly a grave complication. Ventricular tachycardia refractory to all available therapy is a rarity nowadays, except as a terminal event in a dying heart.

The purpose of this communication is to describe a case in which a recurring ventricular tachycardia occurred in a patient who had suffered a cardiac

infarction some weeks previously. The arrhythmia was refractory to all modes of therapy and caused severe deterioration of haemodynamic function. The tachycardia responded finally to revascularization of the ischaemic myocardium by an aorto-coronary saphenous vein bypass graft. As far as we are aware, this is the only case in whom this operation has been performed for intractable life-threatening arrhythmia due to coronary artery disease. The favourable outcome is further evidence for the beneficial effects of this procedure on the function of ischaemic cardiac muscle.

Case report

Mr J.F. Age 61 years. First presented on the 14 March 1972, with an acute inferior myocardial infarction confirmed electrocardiographically (Fig. 1). On admission to the intensive care unit he suffered a cardiac arrest in ventricular fibrillation. This proved resistant to repeated DC defibrillation. Stable rhythm was finally achieved following administration of 1 mg of propranolol intravenously and subsequent DC shock. The following day he had an attack of ventricular tachycardia at a rate of 150/min, which responded to intravenous lignocaine (75 mg) and sedation with Diazepam and amylobarbitone.