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A fatal reaction to diazoxide

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DIAZOXIDE has been available for over 5 years for the treatment of hypoglycaemia from any cause. This is the first published report of a fatal reaction to the drug.

Case report

A 58-year-old spinster was first seen in April 1967 complaining of cough and dyspnoea following a chest infection 4 months previously.

On examination she was found to have atrial fibrillation, mitral stenosis and a large right pleural effusion. The fluid was bloodstained and contained no malignant cells. The effusion was thought to be due to pulmonary infarction, so she was treated with anticoagulants and her dyspnoea improved.

In July 1967 she still had radiological evidence of a right pleural effusion but aspiration was unsuccessful, suggesting collapse of part of the right lower lobe. In October 1967 Mr G. Keen performed a closed mitral valvotomy from which she made a good recovery.

One month later she became confused and sweaty at about 06.00 hours on several consecutive mornings and the blood sugar during an attack was found to be 20 mg/100 ml.

Further investigation revealed a persistently low fasting blood sugar and plasma insulin (10 μ U/ml) neither of which was raised by glucagon, 1 mg i.v. A 6-hr glucose-tolerance curve (Fig. 1) showed diminished glucose tolerance with early and late hypoglycaemia. Tolbutamide 1 g i.v. and glucose 50 g by mouth produced a normal rise in plasma insulin from 10 μ U/ml (fasting) to 50 μ U/ml in 10 min. A normal level of 'insulin-like activity' was also found.

FIG. 1. Six-hour glucose-tolerance curve.

The conclusions drawn from these investigations were that there was no evidence of an insulinoma and that she probably had an extra-pancreatic tumour which was causing hypoglycaemia. There was no mass in the abdomen and bronchoscopy was normal. As the site of the tumour was not obvious she was treated with prednisone in an attempt to raise her blood sugar sufficiently to prevent her symptoms. Five milligrams nightly had no effect, but 60 mg/day abolished her symptoms and her fasting blood sugar rose to 70 mg/100 ml. After 10 days the dose was reduced to 30 mg daily and continued for 5 weeks during which time she had no hypoglycaemic reactions whatsoever. This naturally caused undesirable side effects, so the drug was withdrawn and treatment with diazoxide 100 mg t.d.s. was started on 14 March 1968 (see Table 1). Two days later there was no improvement, so bendrofluazide 10 mg daily was added. The dose of diazoxide was subsequently increased until on 600

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TABLE 1

Date (1968)	Blood sugar (mg/100 ml)	Symptoms		Drugs
		Hypoglycaemia	Fluid retention	
Pre-treatment	25 (fasting)	+		
14 March		+		Diazoxide (300 mg/day)
15 March	50 (11.30 hours)	+		Diazoxide (300 mg/day)
16 March		+		Diazoxide (300 mg/day) and bendrofluazide (10 mg/day)
17 March		+		Diazoxide (300 mg/day) and bendrofluazide (10 mg/day)
18 March		+		Diazoxide (500 mg/day) and bendrofluazide (10 mg/day)
19 March	25 (fasting)	+		Diazoxide (500 mg/day) and bendrofluazide (10 mg/day)
20 March	25 (fasting)	+		Diazoxide (500 mg/day) and bendrofluazide (10 mg/day)
21 March	40 (fasting)	+		Diazoxide (600 mg/day) and bendrofluazide (10 mg/day)
22 March	50		+	Diazoxide (600 mg/day) and bendrofluazide (10 mg/day)
23 March			+	Diazoxide (600 mg/day) and bendrofluazide (10 mg/day)
24 March			++	Diazoxide (600 mg/day) and bendrofluazide (20 mg/day)
25 March			+++	Drugs stopped
26 March	1180 (09.15 hours)			Soluble insulin (10 units i.v.)
	1260 (14.00 hours)			Soluble insulin (30 units i.v.)
	1100 (16.00 hours)			Soluble insulin (80 units i.v.)
	1025 (17.00 hours)			Soluble insulin (100 units i.v.)
	800 (19.00 hours)			
	600 (21.00 hours)			
	480 (22.30 hours)			
27 March	284 (00.30 hours)			

mg/day the symptoms of hypoglycaemia were abolished.

After 3 days on diazoxide 600 mg daily, she had oliguria and gross fluid retention which had failed to respond to increasing the dose of diuretic. Electrolyte levels were: plasma sodium 100 mEq/l, potassium 4.4 mEq/l, chloride 62 mEq/l, bicarbonate 13.5 mEq/l and urea 125 mg/100 ml. Urea and electrolytes prior to treatment were normal. Plasma diazoxide was 5–10 mg/100 ml (semi-quantitative TLC method). Diazoxide was stopped but she became anuric despite intravenous frusemide and mannitol. Blood sugar was 1180 mg/100 ml which was rapidly lowered with i.v. soluble insulin and peritoneal dialysis was started. Two litres of fluid had been removed in this way when after 7 hr she suddenly died.

Necropsy was carried out 7 hr after death. In the lower part of the right pleural cavity there was a large encapsulated solid tumour which weighed 1340 g. Microscopy showed this to be a fairly well differentiated fibrosarcoma with uniform spindle cells and very occasional mitoses. The kidneys were swollen and pale. There was submucosal haemorrhage in the duodenum but the pancreas was entirely

normal. There was evidence of chronic rheumatic heart disease and of successful mitral valvotomy. Other organs were normal.

Discussion

Hypoglycaemia due to fibrosarcoma is now a well-recognized clinical entity. The tumour is retro-peritoneal in 40%, intra-abdominal in 32% and in the pleural cavity in 28% (Lowbeer, 1961). The tumours are invariably large and usually weigh 2–4 kg. The method of production of hypoglycaemia by these tumours is obscure and it is probable that more than one mechanism exists. Diagnosis depends on the presence of fasting hypoglycaemia with a normal level of plasma insulin and a large abdominal or intra-thoracic mass. The principal differential diagnosis is from insulinoma in which plasma insulin levels are elevated both in the fasting state and after tolbutamide.

In this case, the clinical diagnosis was hypoglycaemia caused by an occult extrapancreatic tumour in view of persistently normal levels of plasma insulin. The site of the tumour was not discovered during life as in the chest X-ray (Fig. 2), its superior border was thought to be a high right diaphragm

Fig. 2. Chest X-ray.

secondary to pulmonary infarction and subsequent collapse. Pneumoperitoneum was attempted to outline the right hemidiaphragm but informative pictures were not obtained. No abnormality could be found in the abdomen and as a large tumour was to be expected, exploration was not felt to be justified. She was treated empirically in view of her symptoms and the failure to find a tumour. On large doses of steroids the symptoms were controlled and the fasting blood sugar normal. However, the long term side-effects were unacceptable so treatment with diazoxide was started in view of encouraging preliminary reports on the use of this drug.

Diazoxide is an analogue of the benzothiadiazine diuretics but is in itself antidiuretic. It was originally introduced as a hypotensive agent (Dollery, Pentecost & Samaan, 1962) but it was found to produce hyperglycaemia and glycosuria, and since then its use has been confined to hypoglycaemic states. Diazoxide inhibits secretion of insulin by the β -cells of the pancreas and probably stimulates glycogen degradation and reduces glycogen synthesis. All these effects result in an increase in circulating glucose.

Diazoxide has been used therapeutically in over 100 cases of hypoglycaemia and patients with the following conditions have responded favourably:

- (1) Leucine-sensitive hypoglycaemia.
- (2) Idiopathic hypoglycaemia of infancy.
- (3) Functional islet-cell tumours whether benign or malignant.

- (4) Extra-pancreatic neoplasms producing hypoglycaemia.
- (5) Glycogen storage disease.
- (6) Hypopituitarism.
- (7) Hypoglycaemia of unknown origin.

Dosage in children has varied from 5 to 20 mg/kg body weight/day and in adults from 300 to 1000 mg/day. Concomitant administration of a thiazide diuretic produces an additional hyperglycaemic effect in 25% of cases.

The action of the drug is rapid and brief. Animal experiments have shown a return of blood sugar to pre-treatment levels within 24 hr of giving the drug, and this has been confirmed in patients undergoing treatment.

Common side-effects of the drug include anorexia, nausea and vomiting and peripheral oedema which may be associated with hyponatraemia. Oedema can usually be controlled by giving a thiazide diuretic in addition. Hirsutism occurs in a minority of patients, and is always reversible. Transient hyperuricaemia may occur but no definite cases of impaired renal function due to the drug have been reported. There have been no serious haematopoietic reactions, and no deaths as a result of the drug have hitherto been reported.

It is curious that the initial response to the drug was disappointing in this patient, yet within 4 days of increasing the dose to 600 mg daily she developed gross hyperglycaemia and fluid retention with oliguria. Although she lived for 2 days after stopping treatment, her condition did not improve. It is difficult to escape the conclusion that the drug was directly responsible for her death.

This case suggests that the dose of diazoxide should be increased rather more cautiously than has been usual in the past. A starting dose of 300 mg/day for adults, increasing by not more than 100 mg/day every 4 days would seem reasonable. Fluid retention must be regarded as potentially dangerous, especially if unresponsive to thiazides. Oliguria, significant hyponatraemia and hyperglycaemia are indications for stopping the drug, at least temporarily.

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