CASE REPORTS

Lactic acidosis and hyperamylasaemia associated with phenformin therapy

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Summary

A case is described of lactic acidosis and hyperamylasaemia in a diabetic with impaired renal function treated with phenformin. Despite normal blood pressure and adequate tissue perfusion, the patient succumbed. No evidence of pancreatitis could be found at autopsy.

Introduction

Lactic acidosis, first described by Clausen (1925), is most frequently seen accompanying hypotension and impaired tissue perfusion, but has been reported in association with many other conditions such as phenformin therapy, non-ketotic diabetic acidosis, ethanol ingestion and glycogen storage disease (Oliva, 1970; *Lancet*, 1973). Recently, an association was suggested between non-ketotic diabetic acidosis, pancreatitis and treatment with phenformin (Levitan, 1973; Coodley, Derasse and Carver, 1973). We report such a patient with severe acidosis, elevated blood lactate and serum amylase, in whom there was no clinical or pathological evidence of pancreatitis.

Case report

A 78-year-old male diabetic controlled by chlorpropamide 500 mg and phenformin (slow release) 100 mg daily was admitted to hospital in August 1971. He was hypertensive and had chronic heart block and congestive cardiac failure due to myocardial ischaemia. He had been treated with methyl-dopa, isoprenaline hydrochloride, frusemide and potassium supplements. There was no evidence of alcohol consumption or hepatic dysfunction, but renal function was impaired, values for blood urea before admission ranging from 70-90 mg/100 ml.

For 3 days before admission he had been drowsy, and on the day of admission he began to vomit.

He was not dehydrated, but was stuporose, with Kussmaul respiration. The pulse rate was 60/min, and the blood pressure 140/80. There were no signs of heart failure and the peripheral tissues were well perfused. The abdomen was soft with no tenderness, and normal bowel sounds. Urine analysis revealed neither glucose nor ketones. The blood sugar was 145 mg/100 ml, blood urea 150 mg/100 ml, serum sodium 137 mEq/l, potassium 5.8 mEq/l, bicarbonate 4 mEq/l, arterial blood pH 7.02, P_{CO_2} 13.7 mmHg, PO_2 115 mmHg, SAO_2 100%, lactate in whole arterial blood 156 mg/100 ml (17.3 mEq/l), serum amylase 1300 Somogyi units/100 ml, and white cell count 12,000 mm^3 .

Following infusion of 600 mEq of sodium bicarbonate over a period of 18 hr, the arterial pH was 7.44, arterial lactate 46 mg/100 ml (5.1 mEq/l) and serum bicarbonate 28 mEq/l. With metabolic correction the level of consciousness improved. There were no clinical features of pancreatitis and the high serum amylase fell sequentially to 400 Somogyi units/100 ml at 12 hr, 230 units at 21 hr and to normal in 36 hr. However, 48 hr later he deteriorated, becoming comatose, hypotonic and areflexic despite normal blood pressure. These events were unattended by metabolic derangement, and death occurred on the sixth day. Autopsy showed extensive midbrain infarction. There was some hyalinization of the islets of Langerhans, but no pancreatitis. A solitary 3 cm stone was present in the gall bladder; the liver showed congestive changes only.

Discussion

While phenformin is known to interfere with cellular aerobic metabolism and thus enhance lactic acid formation, its site of action remains controversial (Oliva, 1970). Since its introduction in 1957 there

have been several reports of lactic acidosis in phenformin-treated diabetes. Most have been in patients with impaired renal function and poor tissue perfusion, thus making it difficult to evaluate the aetiological role of phenformin. The decision to administer phenformin to this patient known to have impaired renal function is contrary to the recommendations of previous authors who have pointed to its potential danger in patients with even minor evidence of renal failure (MacGregor, Poole-Watson and Jones, 1972).

In the case under consideration, phenformin was thought to be the most likely cause of the raised lactate although isoprenaline in high infusion rates has caused small increments in lactate levels (Krasnow *et al.*, 1964). Throughout the period of acidosis the patient's blood pressure remained stable, and despite the underlying ischaemic disease, tissue perfusion, as judged clinically and by the normal urinary output and arterial oxygen saturation, was adequate. Blood lactate levels are normal in uraemia (Tranquada, Grant and Peterson, 1966). The absence of urinary ketone bodies in the presence of a very high blood lactate level indicates that the latter was the major component in the acidosis. However, Alberti *et al.* (1971) have pointed out that lactic acidosis in diabetics may be accompanied by raised blood concentrations of ketone bodies when simple screening tests of serum and urine are negative.

Clinically acute pancreatitis was seen in twelve patients, and elevated serum amylase in an additional seven, in a series of forty-six patients with lactic acidosis (Tranquada *et al.*, 1966). Despite the high mortality, autopsy evidence of acute pancreatitis was not presented. More recent authors (Levitan, 1973; Coodley *et al.*, 1973) have suggested an association between acute pancreatitis and treatment with phenformin. The patients they report were severely acidotic owing mainly, as in our own case, to lactic

acidosis. The diagnosis of acute pancreatitis rested mainly on the raised serum amylase. In a recent analysis of forty-two consecutive episodes of diabetic keto-acidosis, serum amylase was elevated during twenty-five (60%) and in eight (17%) the peak amylase exceeded 1000 Somogyi units/100 ml (Knight *et al.*, 1973). No correlation between hyperamylasaemia and the degree of acidosis was found. We were also able to show that hyperamylasaemia, with or without abdominal pain, does not of itself justify a diagnosis of acute pancreatitis. Similarly, the patient here reported did not have pancreatitis, and the origin of the amylase remains unexplained. There is as yet, no evidence to incriminate phenformin therapy as a cause of acute pancreatitis.

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