MEDICAL MEMORANDA

Lacticacidosis, Ketoacidosis, and Hyperalaninaemia in a Phenformin-treated Diabetic Patient

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Lacticacidosis has often been described in patients with diabetes mellitus, especially those treated with the oral hypoglycaemic agent phenformin (Woods, 1971). Recently severe acidosis due to the accumulation of large amounts of lactic acid and the ketone bodies 3-hydroxybutyrate and acetoacetate has been reported (Barnardo *et al.*, 1970; Marliss *et al.*, 1970; Alberti *et al.*, 1971), and abnormal amino-acid metabolism has also been shown (Marliss *et al.*, 1972).

We describe here a case of normoglycaemic combined lactic-acidosis and ketoacidosis associated with a very high blood alanine concentration. The acidosis was successfully treated with intravenous sodium bicarbonate, glucose, and small doses of subcutaneous soluble insulin.

Case Report

A 57-year-old man was admitted after the sudden onset of left-sided weakness. He had a five-year history of diabetes mellitus treated with diet and chlorpropamide (500 mg/day). One year before admission phenformin (50 mg daily) had been added to this regimen and three weeks before admission the phenformin dose was increased to 50 mg three times a day.

On admission he had a blood pressure of 180/100 mm Hg and a regular pulse of 96/min. There were occasional rhonchi over the posterior chest fields. He was drowsy but able to answer questions. There was left ptosis and a left sixth nerve palsy but no papilloedema. There were bilateral extensor plantar responses, and muscle tone and power were reduced on the left side in all muscle groups. There were no sensory changes.

CLINICAL COURSE

Treatment with chlorpropamide 250 mg twice daily and phenformin 50 mg three times a day was continued. During the next eight days the left hemiparesis became increasingly dense and he became depressed and apathetic. He was started on amitriptyline 25 mg three times a day.

On day eight atrial fibrillation was noted and he was digitalized. Next day he became semi-conscious with an increase in respiratory rate of 35/min with no signs of respiratory disease, cardiac failure, or hypertension. Blood glucose was 115 mg/100 ml, plasma sodium 139 mEq/l, potassium 5.7 mEq/l, chloride 98 mEq/l, and bicarbonate 9 mEq/l. The anion gap was 38 mEq/l, which led to the investigation of the cause of his metabolic acidosis. Arterial pH was 7.13, P_{O_2} 105 mm Hg, and P_{CO_2} 13 mm Hg. Phenformin,

and chlorpropamide therapy were stopped because of the probable diagnosis of lacticacidosis.

METABOLIC INVESTIGATIONS

Blood metabolite determinations showed the presence of a severe lacticacidosis, a marked ketoacidosis, and a thirteenfold increase in blood alanine concentrations (see table). Blood urea was 120 mg/100 ml, SGOT 55 IU/l, and other liver function test results were normal. The lactate:pyruvate and 3-hydroxybutyrate:acetoacetate ratios were both grossly raised. Free flowing venous samples were analysed for metabolites as described previously (Alberti *et al.*, 1972).

Initial Blood Metabolite Concentrations

	Concentration (mmol/l.)	Normal Range (mmol/l.)	Normal Values in Diabetic Patients ($\pm$ S.D.)* (mmol/l.)
Lactate	16.9	0.4-1.2	1.0 $\pm$ 0.4
Pyruvate	0.45	0.03-0.11	0.09 $\pm$ 0.03
3-Hydroxybutyrate	9.9	0-0.096	0.073 $\pm$ 0.114
Acetoacetate	0.44	0-0.031	0.047 $\pm$ 0.048
Alanine	3.92	0.20-0.435	—
Glycerol	0.263	0.02-0.12	0.095 $\pm$ 0.045
Lactate: pyruvate	37.9	7.3-13.3	12.6 $\pm$ 4.2
3-Hydroxybutyrate: acetoacetate	22.4	0.2-2.7	1.6 $\pm$ 2.4

*Values taken from 308 patients attending diabetic clinic (Leite *et al.*, 1974).

TREATMENT AND FURTHER COURSE

During the next 14 hours 600 mEq of sodium bicarbonate were given intravenously. Arterial pH increased to 7.41. Lactate rose further to 24.1 mmol/l, however, and was still 20 mmol/l. at 14 hours (see fig.).

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Total blood ketone body concentration decreased from 10.33 to 6.00 mmol/l. Blood pyruvate rose from 0.45 to 0.56 mmol/l. and alanine from 3.92 to 4.33 mmol/l. The 3-hydroxybutyrate:acetoacetate ratio decreased from 22.4 to 9.2 but the lactate:pyruvate ratio remained unchanged.

Intravenous glucose was begun one hour after the bicarbonate, and 45 g was given in the next 13 hours. Blood glucose rose to 340 mg/100 ml. A small dose of subcutaneous soluble insulin (8 U) was given just after the last bicarbonate. Further doses of 12, 8, and 8 U were given, respectively, 4, 10, and 12 hours later (see fig.). Intermittent insulin therapy was then continued.

During the first 12 hours of insulin treatment arterial blood pH remained stable between 7.38 and 7.41, and blood lactate concentration decreased to 12.74 mmol/l., pyruvate to 0.37 mmol/l., total ketone body concentration to 1.91 mmol/l., and alanine to 2.14 mmol/l. Glucose was infused at a mean rate of 9 g/hr.

Blood lactate, ketone body, pyruvate, and alanine concentrations then fell rapidly and pH rose to 7.56. The lactate:pyruvate ratio was still raised (18.6) 60 hours later, however. Plasma bicarbonate had returned to 25 mEq/l. by 60 hours, when the anion gap was 23 mEq/l.

Twenty-four hours after the start of intensive treatment rectal temperature rose to 38°C, and a right basal pneumonia was diagnosed, which was treated with intravenous ampicillin.

Over the next five days there was a gradual improvement and the patient's mental state returned to normal. The dense left hemiplegia remained. Six weeks later he was discharged, able to walk with the aid of a stick and taking glibenclamide 20 mg/day to control his diabetes. Eighteen months later his diabetes remained well controlled on this therapy.

Comment

In most cases of lacticacidosis in patients taking phenformin other factors have been present, such as diminished renal function (as in our patient), hypotension, dehydration, liver disease, and ethanol ingestion. The importance of renal impairment is that in the normal state half or more of phenformin is excreted unchanged in the urine.

In 34 cases of phenformin-associated lacticacidosis received by Cohen *et al.* (1973) six patients, like ours, had increased their phenformin therapy within the preceding two months.

In our patient ketone body accumulation was sufficient to account for more than one-third of the hydrogen ion accumulation. The blood glucose concentration was normal, which makes the ketoacidosis difficult to explain.

The ratio of blood lactate to blood pyruvate concentration has been related to the intracellular cytosol redox state (Hohorst *et al.*, 1959). The very high ratio in our patient could have been due both to a fall in intracellular pH and to intracellular

anoxia. The ratio may also be altered as a result of a disequilibrium in the relative rates of release and use of lactate and pyruvate by different tissues. There was no clinical evidence of hypoxia, hypotension, or poor tissue perfusion. The lactate:pyruvate ratio remained high for many hours even after correction of the acidosis, casting some doubt on the interpretation of such ratios.

Marliss *et al.* (1972) have found large increases in the plasma concentrations of several amino-acids in patients with lacticacidosis. The largest rise was in alanine concentration with a mean rise ($\pm$ S.D.) of 1.86 ± 0.74 mmol/l., compared with 3.92 mmol/l in our patient. In muscle alanine is in equilibrium with pyruvate through the enzyme alanine aminotransferase.

Alanine is a major glucose precursor and is converted in the liver to pyruvate. When lactate and pyruvate metabolism are inhibited the metabolism of alanine will also be impeded. Further evidence of impaired gluconeogenesis is also provided by the fourfold increase in blood glycerol concentration.

The correction of the acidosis with bicarbonate does not necessarily initiate lactate removal. In our case and those reported by Johnson and Waterhouse (1968) the major part of lactate removal occurred during treatment with insulin and glucose. The mechanism by which this treatment promotes lactate remains unclear. This form of treatment deserves further trial.

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