The Management of Diabetic Coma

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The terms diabetic precoma or coma are used to describe the acute illness that results from lack of insulin. Fully developed coma is uncommon but the state of consciousness is as good a measure as any of the gravity of the situation. Root (1959) regarded a plasma bicarbonate concentration of 9 mEq/litre or less as a sufficient definition but it is increasingly clear that factors other than ketoacidosis may be as great a threat to life. At one extreme are cases of gross acidosis with minimal disturbance of fluid and electrolytes, while at the other are those with little ketoacidosis but profound dehydration. Some of the latter may be distinguished as examples of non-ketotic hyperosmolar coma.

In order to treat diabetic coma it is essential to define the extent of the deficiencies and this implies a well equipped and swiftly acting biochemical service. It follows that there is no place for the treatment of such patients in hospitals that lack this facility, and in most instances the delay of a journey to a large centre is fully justified. If the diagnosis is not in doubt, the doctor who first sees the patient should give an initial dose of 60–100 units of soluble insulin before transfer to hospital but it is essential that a note to this effect goes with him.

CAUSES OF KETOACIDOSIS

Infection is probably the most common cause of ketoacidosis, although it may be difficult to identify its nature. The story of diarrhoea and vomiting at the onset of the attack, which is described by many patients, is unlikely to indicate gastro-enteritis. Respiratory infections and pyelonephritis are the most frequent. Some writers (Cohen *et al.*, 1960; Sheldon and Pyke, 1968) find omission of insulin by the patient to be the principal cause. Undiagnosed diabetes still accounts for a substantial number of cases, particularly among the elderly.

THE PHYSIOLOGICAL ABNORMALITIES IN KETOACIDOSIS

When the supply of insulin is inadequate, glucose is unable to enter many cells, notably those of muscle, and is not used at the normal rate. At the same time, glucose is produced at an increased rate from glycogen and protein so that

hyperglycaemia follows. This leads to heavy glycosuria with osmotic diuresis and consequent loss of water and electrolytes, which is greatly aggravated by vomiting.

Fat metabolism is increased and fat stores are mobilised. Fatty acids are converted to acetyl coenzyme A (acetyl CoA) in the liver, and under normal conditions acetyl CoA unites with oxaloacetate to enter the Krebs cycle or be converted to protein and fat. In ketoacidosis there is a relative deficiency of oxaloacetate associated with conversion of long-chain fatty acids to acetyl CoA thioesters (Wieland, 1965). The mobilisation of fat stores yields acetyl CoA in excess of the available oxaloacetate, and this excess is converted to acetoacetate.

Protein synthesis is depressed in the absence of sufficient insulin and the conversion of amino acids to protein is further impaired by the high secretion rate of cortisol that accompanies ketoacidosis (Nabarro, 1967).

BIOCHEMICAL FINDINGS IN KETOACIDOSIS

Blood glucose is always high but may be little more than 300 mg/100 ml when ketosis is severe. Levels exceeding 1,000 mg/100 ml are not at all rare.

Ketone bodies. Acetoacetate can now be measured on the AutoAnalyzer by the method of Salway (1969). The normal level is around 0·10 mmol/litre but in ketoacidosis exceeds 1·5 mmol/litre and is usually between 2 and 4 mmol/litre. 3-hydroxy-butyrate concentrations are usually greater than 5 mmol/litre but when they lie between 2 and 5 mmol/litre the standard bicarbonate is low but the blood pH is usually normal (Watkins *et al.*, 1970a). Plasma acetone, normally about 0·03 mmol/litre, is greatly increased, usually above 5·0 mmol/litre and occasionally above 12·0 mmol/litre returning only slowly to the normal level (Sulway and Malins, 1970). Rapid testing with Ketostix on a sample of plasma will identify those patients whose acetoacetate level exceeds 2 mmol/litre and 3-hydroxybutyrate 3 mmol/litre (Watkins and FitzGerald, 1968).

Free fatty acids are increased in uncontrolled diabetes, and in ketoacidosis often exceed 2 mmol/litre (the normal range is 0·45 to 0·90 mmol/litre by the method of Duncombe, 1964).

Bicarbonate. The plasma bicarbonate is reduced below 15 mEq/litre but the level does not correlate well with the severity of ketosis.

Hydrogen ion concentration. Arterial pH is reduced in ketoacidosis if it is at all severe and may be as low as 6·80. While very low figures have a grave significance they are compatible with complete recovery.

Serum insulin is low as measured by immunoassay, often less than 25 μu/ml with blood glucose exceeding 300 mg/100 ml.

Electrolytes. Serum sodium and potassium levels are often normal but may be high or low according to the nature of fluid losses during the development of ketoacidosis. The potassium is often moderately raised and occasionally, for no obvious reason, dangerously reduced. The significance of changes in other electrolytes such as phosphate has not been defined.

Urea. The blood urea is elevated in accordance with the degree of dehydration. If urea retention continues after three or four days the possibility of pre-existing renal damage has to be considered.

PRINCIPLES OF MANAGEMENT

Fluid Replacement

The object is to make good an average deficit of 6 litres of water derived in roughly equal proportions from the intracellular and extracellular compartments. In addition, there is a calculated loss of 500 mEq of sodium, 400 mEq of chloride and 350 mEq of potassium (Nabarro *et al.*, 1952). No attempt should be made to achieve this by any other than the intravenous route. The choice of fluid for initial replacement has been much discussed but never generally agreed. In most cases physiological saline, containing 154 mEq/litre of sodium and of chloride, is satisfactory and is only contra-indicated by gravely impaired renal function. More 'correct' is a solution containing 130 mEq of sodium, 100 mEq of chloride and 30 mEq of lactate per litre, although some object to giving lactate when excess may already be present. When hyperosmolarity is extreme, half-normal saline is indicated and seems to be free from risk in the non-ketotic cases, but in those who are ketotic it may lead to cerebral oedema, perhaps due to an over-rapid correction of the hyperosmolarity (Maccario and Messis, 1969).

Potassium

Traditional advice is to delay the administration of potassium until the plasma potassium is known and it is clear that renal function is adequate. It is true that the plasma potassium is usually normal or high before treatment is begun but low levels, sufficiently depressed to threaten life, are being recognised with increasing frequency (Abramson and Arkey, 1966; Watkins *et al.*, 1970b). Since the level is bound to fall once treatment is under way such a situation is highly dangerous. If the plasma potassium is unknown and the patient is in a grave condition it is not a risky procedure to give 1 g (13 mEq) of potassium chloride in the first hour of treatment.

As soon as fluid is restored and insulin takes effect, potassium begins to enter the cells once more and the plasma level may fall very sharply. If there is a flow of urine, potassium chloride should be given at a rate of 2 g an hour

and a total of 5 to 25 g may be needed. It is often possible to complete the replacement by the oral route in the form of orange juice.

Bicarbonate

The rapid correction of acidosis by giving bicarbonate is said to cause clinical improvement, facilitate insulin action, and save lives (Hudson *et al.*, 1960). However, enthusiastic administration of intravenous sodium bicarbonate (8·4 per cent) may cause an acute drop in plasma potassium at a time when the level is already beginning to fall. This treatment should be confined to those who are extremely acidotic since the acidosis is relieved quite rapidly in the normal way when insulin begins to take effect and the flow of ketones from the liver subsides. The bicarbonate may be given after the first litre of saline at the rate of 100 to 150 mEq in an hour or in single doses of 50 mEq over a period of 15 minutes.

Glucose and Fructose

There is general agreement that intravenous glucose has no place in the treatment of ketoacidosis, at least until the late phase of recovery when the possibility of hypoglycaemia arises. The alternative use of fructose was suggested because some tissues are able to use it without the aid of insulin. It has not proved effective and much of the fructose is converted to glucose (Rosecan and Daughaday, 1954).

Insulin

In diabetic ketoacidosis there is always a degree of insulin resistance but there is no general agreement on the best dosage schedule. It must be adequate but should avoid extremely rapid reduction of the blood sugar which may cause acute electrolyte shifts and a change in osmolarity. For a severe case an initial dose of 200 units, half intramuscular and half intravenous, is not excessive. Intravenous doses of less than 60 units are probably of little value since much of the injected insulin is lost. A dosage based on the blood sugar level is not satisfactory since the degree of ketoacidosis is by no means related to the height of the blood sugar, particularly in those hyperosmolar cases with extreme hyperglycaemia. It is, however, necessary to know the blood sugar reading before insulin is given so that the effect of the initial dose can be measured when the 1- and 2-hour blood sugars are recorded. If there is little change—not more than 100 mg/100 ml—the original dose is repeated. If the fall is significant the amounts of insulin are reduced to one half of the first dose, or the second injection may be delayed until 4 hours. At this point there should be clear evidence of insulin effect in the blood pH, glucose, and

ketones and if this is not apparent much increased amounts of insulin are necessary. A further assessment at eight hours usually makes it possible to revert to subcutaneous insulin only, and in relatively modest doses (40 to 60 units).

The danger of hypoglycaemia after large doses of insulin is not great under hospital conditions with frequent blood sugar estimations. On the other hand, the risk of a drift back to ketoacidosis once the intensive regime is relaxed is considerable, particularly in the period from 12 to 24 hours after admission.

OUTLINE OF PRACTICAL MANAGEMENT OF KETOACIDOSIS

There is a good case for admitting these patients to the intensive care unit since problems with blood potassium may arise at an early stage and from every viewpoint it is essential that they should never be left unattended. Electrocardiograph monitoring is desirable.

Along with the initial samples for blood sugar, electrolytes, urea, bicarbonate, pCO_2 and pH a specimen is retained for immediate centrifuging so that Ketostix may be applied to the plasma (Watkins and FitzGerald, 1968). If the reaction is strongly positive it is almost certain that the acetoacetate level exceeds 2 mmol/litre and the 3-hydroxybutyrate 3 mmol/litre; this degree of ketosis is highly significant. The Dextrostix test will inevitably indicate a blood sugar above 200 mg/100 ml. The urine must be examined. In severely ill patients catheterisation is justified and may be necessary to measure the rate of urine formation which has an important bearing on the replacement treatment.

In all but the mildest cases the stomach is dilated, containing a large quantity of brown fluid and must be emptied by a Ryle's tube. There is a real risk of sudden vomiting, with fatal inhalation.

Intravenous replacement of fluid begins immediately with physiological saline or saline/lactate, remembering the possibility that potassium will be needed as soon as the result of the blood estimation is known. Two litres are given as fast as possible and 1 to 2 litres an hour until dehydration lessens; a total of 6 to 8 litres in the first 24 hours is usual. Even when there is extreme circulatory collapse it is probably valueless to use plasma expanders in place of the saline solutions. The circulation may be overloaded in the elderly but this is unusual even with rapid rates of administration.

One indication of improvement is a flow of urine, and this relieves anxiety about the administration of intravenous potassium. Rarely, oliguria persists and signifies tubular necrosis.

The initial quantity of insulin may be determined by the clinical severity

of the acidosis, subsequent doses being related to the rate of fall of the blood sugar.

Penicillin is given routinely unless there is a clear indication for some other antibiotic. It can be very difficult to detect infection clinically in these very ill patients.

During the phase of recovery every effort is made to determine the cause of the attack.

NON-KETOTIC HYPEROSMOLAR COMA

Since the description of diabetic stupor without ketosis by Sament and Schwartz in 1957 the syndrome of severe hyperglycaemia, hyperosmolarity of the blood and dehydration without ketoacidosis has been recognised with increasing frequency. Cases of diabetic ketoacidosis range from those with extreme acidosis and little dehydration to those with minimal ketosis and gross dehydration, but non-ketotic hyperosmolar coma seems to be a separate condition in its own right. It has been recognised as a complication of burns (Arney *et al.*, 1960), corticosteroids (Spenney *et al.*, 1969) haemodialysis (Potter, 1966) and acute pancreatitis (Davidson, 1964).

The patients are often elderly but age is of no diagnostic importance and the condition has been recorded in a child of eighteen months (Ehrlich and Boin, 1967). In Britain, the coloured immigrant population provides an unduly large proportion of the cases. The majority are not already known to have diabetes and, if it has been recognised, it has been considered mild. On admission in stupor or coma there is evidence of extreme dehydration without air hunger. Convulsions are common and neck stiffness, nystagmus and exalted or depressed tendon reflexes may be misleading. The haematocrit value is high, the plasma osmolarity above 300 mosmol/litre and the blood sugar commonly above 1,000 mg/100 ml, occasionally as high as 3,000 to 4,000 mg/100 ml. The plasma bicarbonate as a rule lies between 20 and 30 mEq/litre while ketonuria and hyperketonaemia are absent.

The pathogenesis of this condition has not been adequately explained. The most favoured theory is that the amount of circulating insulin is sufficient to inhibit lipolysis in adipose tissue but not for the required increase of peripheral glucose utilisation (McCurdy, 1970). However, free fatty acid levels in the plasma are nearly always elevated and not unlike those in ketotic patients (Watkins *et al.*, 1970a), while triglyceride is modestly raised. Immunoreactive insulin is subnormal but detectable, growth hormone is suppressed and cortisol increased (Vinik *et al.*, 1970). These authors suggest that there may be alternative mechanisms of free fatty acid metabolism by the liver.

The first requirement of treatment is to replace water, which is best achieved

by the use of hypotonic (half normal) solutions of saline. As much as 20 litres of water may be retained in the first 24 hours. When the blood glucose has fallen significantly, 5 per cent dextrose in water may be substituted. Potassium levels should be carefully watched and it may be necessary to give intravenous potassium at an early stage. Insulin dosage should be modest, perhaps 60 units intravenously at the start, and the total may not exceed 150 units in the first 48 hours. There is a risk of precipitating cerebral oedema by enthusiastic treatment and rapid lowering of the blood sugar which may alter too acutely the osmotic gradient between the blood and the cerebrospinal fluid.

The death rate remains depressingly high, probably 30 to 40 per cent overall. A considerable proportion of this mortality is at present almost inevitable because the initial situation and, in particular, depression of the sensorium indicate serious underlying organic defects which persist in spite of treatment.

LACTIC ACIDOSIS

Metabolic acidosis not associated with ketosis but resulting from 'unidentified organic acids' was recognised by Bock *et al.* (1923); lactic acidosis is one of the causes of this 'unmeasured anion' or 'anion gap' (Waters *et al.*, 1963). Two types have been distinguished. In one, lactic acid is slightly above the normal, 0·5 to 1·0 mmol/litre and the lactate/pyruvate ratio of 10/1 is maintained. This is seen in many patients in hospital or may follow infusions of bicarbonate or saline. In the other type, lactate is greatly increased, often above 7·0 mmol/litre but there is no corresponding increase in pyruvate so that the lactate/pyruvate ratio exceeds 10/1. This situation occurs in the presence of tissue hypoxia or, occasionally, as an apparently spontaneous phenomenon (Huckabee, 1961).

Phenformin has been shown experimentally to increase anaerobic glycolysis but only in concentrations which do not occur *in vivo*. A combination of alcohol and phenformin can cause a rather severe rise in blood lactate (Johnson and Waterhouse, 1968).

In cases of suspected diabetic ketoacidosis the contribution of lactate to the acidosis is usually small but often exceeds 3·0 mmol/litre and at times may be entirely responsible for the acid-base changes (Watkins *et al.*, 1969).

The diagnosis of lactic acidosis depends on measurement of lactate and pyruvate but may be suspected when a profound fall of serum CO_2 and pH is associated with levels of ketone bodies that are not high enough to explain it.

The treatment of lactic acidosis is often unsatisfactory because the condition is associated with grave illness but large amounts of bicarbonate (not less than 1,000 mEq/litre in 24 hours) are generally recommended. THAM

(tris-hydroxymethyl aminomethane), an organic buffer, is of dubious efficacy as is methylene blue which is given to convert lactate to pyruvate.

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